



ERS | *monograph*

Pulmonary Complications of HIV

Edited by
Charles Feldman,
Eva Polverino and
Julio A. Ramirez

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Editor in Chief
Tobias Welte

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Preface

Tobias Welte, Editor in Chief

According to figures from UNAIDS, there were 34.2 million people living with HIV in 2011, a rise of 5.1 million on 2001. Of these, 2.5 million had become newly infected, a reduction of 22% on figures from 2001. 1.7 million people died from AIDS-related causes in 2011, a decline of 11% on the number of AIDS-related deaths in 2001. A similar decrease in new infections was seen amongst neonates and infants: from 570 000 in 2003 (when figures peaked) to 330 000 in 2011. However, it must be acknowledged that these are global figures and they hide a wide diversity in the number of cases and deaths between countries and risk groups. The most affected continent continues to be sub-Saharan Africa, followed by Eastern Europe and the Caribbean, and the following groups are disproportionately affected: men who have sex with men, female sex workers, injecting drug users, truck drivers, fishermen and the military [1].



Tremendous progress has been made during the last decade, not only in preventive measures but also in HIV treatment. 25 antiretroviral drugs have been licensed for HIV treatment and, thanks to international financial aid and a reduction in the price, these drugs are now available in low- and middle-income countries. More than 8 million individuals are now on therapy in low- and middle-income countries, and as a result, the death rate in some of the hardest hit countries has started to decline, following mortality reductions in the USA and Europe in the late nineties. The life expectancy of an HIV-infected individual who is receiving treatment is approaching that of an uninfected individual, although there are side-effects of the treatment that have an influence on quality of life and the ability to work and participate normally in daily life [2].

That said, progress in the treatment of AIDS has led to carelessness, especially in western capitals. Important precautions are being forgotten and a rise in new infections has been observed during recent years.

Pulmonary manifestations represent one of the major AIDS complications and are the most life-threatening amongst those

with AIDS. In parallel to the progress in HIV treatment in general, new diagnostic and therapeutic possibilities have recently been developed for various HIV-associated pulmonary complications. This issue of the *ERS Monograph* summarises the current practices and new developments in the prevention, diagnosis and treatment of HIV-related pulmonary complications. I want to congratulate Charles Feldman, Eva Polverino and Julio Ramirez on the tremendous work they have done in compiling this excellent *Monograph*. This book should be of interest to everybody involved in HIV management worldwide. I hope it will stimulate joint research for a better understanding of and more successful therapy for HIV-related pulmonary infectious diseases.

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Guest Editors

Charles Feldman

Charles Feldman is currently the Professor of Pulmonology, Chief Physician, and Head of the Pulmonology Division at the Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand (Johannesburg, South Africa).

He received his undergraduate degree (MB BCh) from the University of the Witwatersrand in 1975. Following his internship at Johannesburg Hospital, he specialised in internal medicine, receiving his FCP (SA) in 1981. In 1993 he was registered as a pulmonologist. He was awarded his FRCP (UK) in 1997. His additional postgraduate degrees included a PhD (1991) and a DSc (2009) from the University of the Witwatersrand, both of these on the basis of a thesis in the field of CAP.



Charles Feldman has been active in both national and international societies. He has been President of the South African Thoracic Society (SATS) on two previous occasions, and is currently a member of the Executive Committee of the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA), a federation that represents all of the individual infectious disease societies in South Africa. He is also Editor-in-Chief of the Federation's Journal, the *Southern African Journal of Infectious Diseases*. Internationally, Charles Feldman has acted as the national delegate for South Africa for the European Respiratory Society (ERS), and in 2014 he was made a Foundation Fellow of the ERS in recognition of his sustained research in the field of respiratory diseases. He is also an active member of the American College of Chest Physicians (ACCP) and the American Thoracic Society (ATS).

Charles Feldman's research is translational and his interest is primarily in the field of CAP, particularly pneumococcal pneumonia, especially in the setting of HIV infection. His basic research has focused on the interactions between the various factors that play a role in the pathogenesis and outcome of pneumococcal infections, namely, the microorganism and its virulence factors, the various host defence mechanisms, and the

commonly used antimicrobial agents. As part of his clinical research, Charles Feldman has contributed to various multicentre international collaborative studies investigating multiple aspects of CAP.

Charles Feldman's research has been published more than 300 times, as books, book chapters, articles and abstracts. He has presented at more than 300 congresses, almost half of them international.

Eva Polverino



Eva Polverino is an expert in respiratory infections and is Senior Investigator at the Hospital Clinic of Barcelona (IDIBAPS, University of Barcelona, Barcelona, Spain) and Associate Professor at the University of Barcelona.

She graduated in Medicine at the University of Naples (Naples, Italy) and went on to specialise in pulmonology at the University of Pisa (Pisa, Italy). After a training period at the Hospital Clinic of Barcelona focusing on gas exchange, she gained a PhD in cardiopulmonary pathophysiology at the University of Pisa. In 2007 she moved to the Department of Pulmonology at the Hospital Clinic of Barcelona, working in the field of respiratory infections.

Eva Polverino is an active member of several respiratory societies: the European Respiratory Society (ERS), the American Thoracic Society (ATS), the Sociedad Española de Neumología y Cirugía Torácica (SEPAR), and the Catalan Society of Pulmonology (SOCAP). She is currently Chair of the ERS Respiratory Infections Group, Co-Chair and member of the Steering Committee of the European Registry and Clinical Research Collaboration in Bronchiectasis (EMBARC), and Chair of the European task force on adult non-CF bronchiectasis (ERS 2014).

Eva Polverino has been an oral session facilitator and speaker at many European, American, Latin-American and Italian respiratory congresses. She has presented more than 150 oral communications at scientific congresses/courses and more than 200 communications (abstracts, posters, *etc.*).

Eva Polverino's personal research interests focus on respiratory infections and particularly CAP, healthcare-associated CAP, cystic fibrosis and non-cystic fibrosis bronchiectasis, and humoral immunodeficiencies, with particular attention to epidemiology, risk factors, outcome, treatment and prevention of the most relevant respiratory infections.

Julio A. Ramirez

Julio A. Ramirez is the Chief of the Division of Infectious Diseases, Professor of Medicine and the Director of the Infectious Diseases Fellowship Training Program at the University of Louisville School of Medicine (Louisville, KY, USA).

He received his medical degree and internal medicine training at La Plata National University School of Medical Science (La Plata, Argentina). He went on to complete: a fellowship in critical care medicine at the National Institute of Respiratory Diseases and Thoracic Surgery at the University of Chile (Santiago, Chile); a residency in internal medicine at the Lincoln Medical Center, New York Medical College (New York, NY, USA); and a fellowship in infectious diseases at the University of Louisville School of Medicine. He is board certified in internal medicine and holds a subspecialty certification in infectious diseases.

Julio Ramirez's research interests include clinical research in the field of pneumonia, and basic research in the field of diagnosis and pathogenesis of infections due to atypical pathogens. He has more than 100 publications in these areas, in journals such as *Annals of Internal Medicine*, *Archives of Internal Medicine*, *Clinical Infectious Diseases* and *Chest*. He is also a reviewer for several journals including the *New England Journal of Medicine* and *Annals of Internal Medicine*.

Julio Ramirez has served as a member of the American Thoracic Society (ATS) committee for the development of national guidelines for the management of CAP, and has served as a member of the Food and Drug Administration advisory committee for anti-infective drugs. He is also a Fellow in the American College of Physicians (ACCP).



Introduction

Charles Feldman¹, Eva Polverino² and Julio A. Ramirez³

Despite significant advances in the overall management of patients, including the use of various preventative strategies, chemoprophylaxis and ART, the burden of disease worldwide that is due to HIV infection remains high, particularly in low-income countries. The major impact of HIV infection falls on the respiratory system, with the spectrum of conditions that complicate HIV infection spanning a myriad of respiratory conditions. These include both infectious diseases (particularly TB, CAP, PCP and various other opportunistic infections) and noninfectious diseases (such as COPD and asthma, bronchiectasis, lung cancer, diffuse parenchymal lung disorders and pulmonary vascular disorders).

While ART has had a very positive impact on the management of HIV infection, patients still continue to develop complications that are related to HIV infection, many of which are linked with lifestyle, such as ongoing smoking, alcohol consumption and drug use. The introduction of ART itself may occasionally be associated with the development of respiratory and systemic manifestations as a consequence of IRIS.

It is therefore with delight that we introduce this *Monograph*, which comprehensively addresses the very numerous and diverse conditions that may be associated with and complicate HIV infection. The chapters span the spectrum of infectious and noninfectious diseases, and address issues both in paediatric and adult populations. Each of the 19 chapters is written by acknowledged experts in the field and provides a comprehensive description of the conditions associated with HIV infection. The authors provide state-of-the-art updates on the different areas discussed, and many chapters include recommendations for the management of the various conditions. Topics discussed include: the epidemiology of HIV infection; current antiretroviral recommendations; communicable and non-communicable diseases and their treatment and prevention; HIV infection in pregnancy, and the diagnostic and therapeutic implications for the newborn; complications in paediatric practice; transplantation; and IRIS in patients on ART.

It is becoming increasingly common for physicians to encounter patients with HIV infection in their daily practice, and it is hoped that this *Monograph* will provide an interesting and informative insight into the various complications that may occur in these patients.

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List of abbreviations

ART	Antiretroviral therapy
BCG	Bacille Calmette–Guerin
CAP	Community-acquired pneumonia
cART	Combination antiretroviral therapy
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
EBV	Epstein–Barr virus
FEV ₁	Forced expiratory volume in 1 s
FVC	Forced vital capacity
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
IFN	Interferon
IL	Interleukin
IRIS	Immune reconstitution inflammatory syndrome
LIP	Lymphocytic interstitial pneumonia
LRTI	Lower respiratory tract infection
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PAH	Pulmonary arterial hypertension
PCP	<i>Pneumocystis jirovecii</i> pneumonia
PCV	Pneumococcal conjugate vaccine
PH	Pulmonary hypertension
PPV	Pneumococcal polysaccharide vaccine
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
TB	Tuberculosis
TMP-SMX	Trimethoprim-sulfamethoxazole
TNF	Tumour necrosis factor



The global epidemiology of HIV

Willem Daniel Francois Venter

HIV arose in Africa and, during the past century, has established itself in very different communities throughout the world. Sexual transmission continues to be the predominant mechanism of transmission, with mother-to-child, intravenous drug use and iatrogenic spread being less common contributors in most settings. Prior to effective ART, the virus placed a huge burden on morbidity and mortality. Although understanding of the transmission of the virus has evolved, there has been continued spread of the virus in the poorer and more marginalised areas of society. Application of new prevention technologies, including the use of antiretrovirals to effectively stop transmission, may be limited by the complex and evolving epidemiology, as well as the cost and political will to tackle affected communities that have historically not had access to healthcare interventions.

HIV is unique, and is the major new global infectious disease of our time. The virus has affected both developed and developing countries worldwide, placing a huge burden on mortality and morbidity prior to the widespread availability of ART, which has transformed the natural history of the disease. The epidemiology of HIV is complex, with different patterns of transmission at different times and in different geographical locations and risk groups. The long lag-time between infection and the symptomatic phase, as well as the wide individual variation in terms of disease progression, made initial and subsequent transmission studies difficult, with limited prevention success to date. HIV may be the most studied disease in modern times. Billions of dollars of research money has been invested since the initial discovery of the first clinical cases through research organisations, such as the US National Institutes of Health (NIH), foundations and governments, with knock-on benefits in the understanding of general immunology, as well as yielding potent anti-hepatitis virus medications [1, 2].

At present, it is estimated by UNAIDS that 39 million people have died of AIDS and that 35 million people are now living with HIV, 13 million of whom are on antiretrovirals. Life expectancy and quality of life of people living with HIV have returned to near normal. First-line therapy is now available in a single tablet with minimal side-effect, and is available in most areas worldwide, representing one of the most significant advances in medical history (fig. 1) [3, 4].

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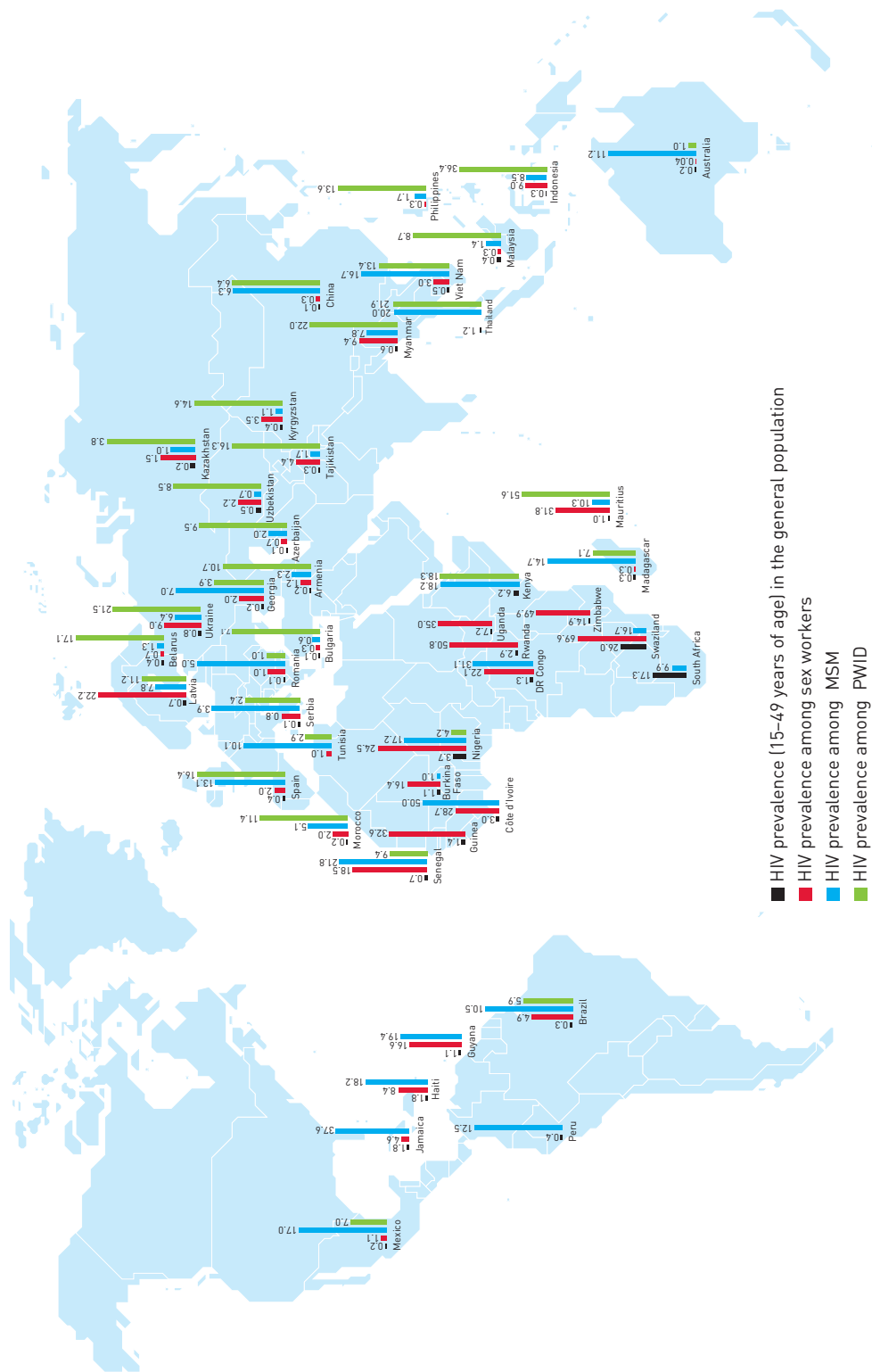


Figure 1. HIV prevalence in adults and key populations. Worldwide, HIV disproportionately affects sex workers, men who have sex with men (MSM) and people who inject drugs (PWID). DR: Democratic Republic. Reproduced from [3] with permission from the publisher.

Origins and initial epidemiology

HIV-1 arose in Africa as the inter-species transfer of a virus between chimpanzees and humans, during the late 19th century. Simian immunodeficiency viruses (SIVs) are well-adapted passenger viruses in primates. SIV does not appear to cause disease or progressive immunodeficiency in most primates, and much interest has focused on the genetic reasons for the control of a virus that shares such homology with its human counterpart. However, the chimpanzee precursor to HIV-1, SIVcpz, appears to cause a similar syndrome in chimpanzees. The virus probably translocated from chimpanzees to humans *via* blood during the hunting or preparation of meat. Early speculation that it originated from the development and distribution of the polio vaccine has been firmly disproved, as have many other assorted theories ranging from conspiracy theories involving escaped laboratory experimental viruses, to aberrant immunological reactions to semen and amyl nitrites commonly used in gay communities in the 1980s. The exact location of the transfer has been mapped by virologists through complex mathematical modelling, based on genetic mutation rates and the identification of numerous stored blood samples obtained decades ago, and has been traced to in and around Cameroon. Initially, it appears to have been restricted to a few villages, before being established in nearby newly established Kinshasa, Democratic Republic of Congo [5, 6].

HIV-2 is much less common and is largely confined to central and west Africa, but appears to be becoming extinct. The virus, which is thought to have arisen from a SIV form found in sooty mangabey monkeys, failed to establish itself more broadly as it appears to be less transmissible. It is also less pathogenic and, although clinically similar, the disease course is longer [7]. For the purposes of this chapter, “HIV” will refer to HIV-1.

Following the establishment of HIV in Kinshasa, the spread of HIV within Africa is somewhat speculative. A recent publication has postulated that syphilis and trypanosomiasis screening and treatment programmes, where a single needle was used hundreds of times to obtain blood for testing or to administer medication, may have led to the establishment of HIV in central and eastern Africa in the mid-20th century [7]. The high mortality rates of the two diseases among workers on railways and other large colonial infrastructure projects motivated employers to seek ways of screening and treating their workforce. Case reports of jaundice soon after screening or treatment in this manner suggest that inoculation of HBV occurred; hepatitis B was widely prevalent in these areas but was still not recognised as a blood-borne virus. It seems highly plausible that this was an efficient mechanism for establishing HIV within the region [7]. Interestingly, HIV prevalence is different in several countries in central Africa, with some having far lower prevalence rates than those further south, suggesting some genetic or other factors impact on the efficiency of transmission.

The dissemination of HIV in the mid-to-late 20th century

The disease steadily spread south in Africa, firmly establishing itself among heterosexual populations within these countries. Some countries, such as South Africa, with firmly shut borders during the apartheid era, and Mozambique and Angola, which may have been protected by having almost nonexistent transport infrastructure, limited the movement of HIV-positive populations and initially restricted the spread. Large seroprevalence surveys in South Africa and Mozambique showed virtually 0% seroprevalence in the early and mid-1980s, in an era where the disease had strongly established itself in areas such as Uganda and surrounding countries [8, 9]. By the early 1990s, in one of the fastest descriptions of an increase in the epidemic, South Africa had a prevalence that was higher than almost all of the

central, eastern and western African countries. By the end of the 1990s, the disease had become firmly established among heterosexual communities throughout Southern Africa, with prevalence rates exceeding 30% in most antenatal clinics [8, 10–11].

The spread into Europe, the Americas and the rest of the world probably arose due to the rise in accessible air travel during the 1970s, coinciding with a sexual revolution within gay communities asserting their right to be open about their sexuality. The use of heroin and other intravenous drugs led to the establishment of HIV in a completely different community within a variety of countries, including Europe, Asia and South America. Haemophiliacs were also one of the first communities affected by HIV. The then revolutionary approach to severe haemophilia was to use pooled plasma for treatment, exposing them to thousands of different donors. Many blood donations were from paid *i.v.* drug users, especially in the USA, meaning that many haemophiliacs were infected [8, 12].

Medical recognition

HIV was first recognised due to the relatively sophisticated disease surveillance present in the USA in early 1980, when a clustering of Kaposi's sarcoma and PCP cases was identified on both coasts. The common abnormalities seen on haematological analysis of lymphocytes alerted the Centres for Disease Control and Prevention (CDC) to the possibility of a common aetiology. The establishment of large cohorts of gay men at high risk in the USA through NIH funding, even prior to the identification of the virus in 1983, allowed for a rapid understanding of the natural history of the disease and the correlation of clinical symptoms with the CD4⁺ lymphocyte count, and later with HIV viral load, using stored samples from these men [8, 12].

These understandings were quickly adapted to staging systems for epidemiological purposes by the CDC and World Health Organization (WHO), and were subsequently adapted to clinical staging, which was initially used for the initiation of treatment of opportunistic infection and later for the initiation of ART [8, 12].

The natural history of HIV and its impact on epidemiology

Following transmission, the acute seroconversion phase of HIV correlates with extremely high viraemia and may last for several months, with some studies suggesting this relatively brief phase may account for half of all transmissions. Transmission, either through sexual exposure, blood or other body fluids, is many times more efficient than normal during this period. Clinical symptoms are usually absent or mild, transitory and nonspecific although, occasionally, they can be severe and tend to be prior to antibody conversion. The understanding that this phase has such transmission importance has transformed the epidemiological understanding, and presented challenges in terms of disease control. Finding highly infectious HIV seroconverters may allow for interventions to stop transmission. Public health approaches to try to identify this group have been hindered by several major challenges: 1) the lack of a cheap, simple test to identify the initial weeks of the infection, when the conventional antibody-based ELISAs remain negative prior to antibody generation; 2) the nonspecific viral symptoms associated with acute HIV infection, meaning that healthcare workers rarely identify the illness; 3) the problems of identifying and implementing screening programmes in risky populations, which are often hidden; 4) the need for follow-up and contact tracing; and 5) the problems of offering evidence-based

prevention interventions. Some US states have instituted successful programmes, but they are expensive and complex to maintain [13–15].

In the absence of antiretrovirals, the time from seroconversion to symptomatic AIDS and death is generally around 10 years. There is wide variance in the length of this period, probably reflecting host genetic ability to control the virus. Infectiousness during the chronic, asymptomatic course of the disease is far lower, again related to the viral load in the bloodstream whatever the transmission route. HIV-positive children often progress to AIDS very rapidly, while slower progressors exhibit a clinical course similar to adults, but are often left with irreversible stunting [1].

Epidemiology of transmission

HIV is largely spread through sexual contact, although mother-to-child transmission (MTCT) and *i.v.* drug use drive specific epidemics in different parts of the world. Safer blood transfusion practices have removed the risk in developed and many developing countries, although unscreened blood is still used in some poorer countries and may pose a transmission risk (table 1) [1, 16].

Sexual transmission of HIV

The transmission of HIV during sex is increasingly being understood at a cellular level, allowing for the development of preventative technologies designed to interrupt transmission

Table 1. HIV transmission risk: estimated per-act probability of acquiring HIV from an infected source by exposure act[#]

Type of exposure	Risk per 10 000 exposures
Parenteral [17]	
Blood transfusion	9250
Needle sharing during injection drug use	63
Percutaneous (needle-stick)	23
Sexual [17]	
Receptive anal intercourse	138
Insertive anal intercourse	11
Receptive vaginal intercourse	8
Insertive vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other[†]	
Biting	Negligible [18]
Spitting	Negligible
Throwing body fluids, including semen or saliva	Negligible
Sharing sex toys	Negligible

[#]: factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection and high viral load, and factors that may decrease the risk include condom use, male circumcision, ART and pre-exposure prophylaxis; none of these factors is accounted for in the estimates presented in the table. [†]: HIV transmission through these exposure routes is technically possible but unlikely and not well documented. Reproduced from [16] with permission from the publisher.

from positive to negative partners. Poor understanding of which specific sexual risk behaviours are associated with increased transmission, coupled with limited understanding of how the epidemic evolved, has limited the impact of many nonbiological behavioural change programmes. Anal sex between heterosexual and homosexual couples confers by far the highest risk of HIV transmission, while the risk from vaginal sex is much lower. Other forms of sex confer negligible risk. Medical male circumcision (as distinct from traditional, cultural/religious, male circumcision) has been shown to be significantly protective, although it can be a complex intervention, and is only partially protective, but is a useful mechanism to link males to healthcare, which has been a consistent problem across HIV programmes (table 1) [1, 16, 17].

Heterosexual sex between serodiscordant couples accounts for the vast majority of infections throughout Africa and a significant proportion of infections in many other parts of the world. While transmission through vaginal sex is relatively ineffective, especially during the chronic phase of the infection when viral loads are low, there is emerging evidence that the risk per conjugal act is higher within southern African communities, for as yet unknown reasons, but which may include background diseases such as ulcerative sexually transmitted diseases, or genetic or even environmental reasons. Alternative explanations for the vast difference in HIV prevalence between southern Africa and the rest of the world have included different sexual behaviours, including distinct forms of sexual partnering such as concurrency, where sexual partnerships overlap, and have been controversial. HIV acquisition risk is clearly dependent on the number of sexual partners, but geography seems to play a much larger role, suggesting a genetic or environmental role [1, 11, 19, 20].

Homosexual male sex accounts for a large proportion of the HIV epidemic in most developed countries, and there has been recent concern regarding the number of new infections in these communities. In the USA, the epidemic is disproportionately racialised, with over half the infections occurring in black men having sex with men, and heterosexual black women. A distinct social phenomenon, known as the “down low”, where men have sexual encounters with other men but do not self-identify as gay, has led to a more scientifically precise term within the HIV world, men who have sex with men (MSM). Those on the down low often have very high risk behaviours, frequently involving unsafe sex with anonymous partners. This has been a major public health problem, and educating this group has been difficult. In addition, it is estimated that the majority of new transmissions occur from people who do not know their HIV status, and hence unknowingly transmit the virus; testing more high-risk groups is a public health priority. Social media have allowed for distinct sexual partnering among different groups, which may involve seeking partners solely for sex. While not confined to gay men, and even though serosorting is common on these platforms, this has been associated with increased risk taking. Within Europe and other developed countries, as well as in South America, the rise in new incident infections has recently fuelled interest in pre-exposure prophylaxis, where antiretrovirals are taken prior to anticipated risky sexual encounters and are highly effective if taken, despite being very expensive. While there is interest in using them among high-risk heterosexuals, such as sex workers, the main current interest is in MSM. In places like Seattle (WA, USA), where many of the studies have been spearheaded, successful rollout of this intervention throughout the city is awaiting evaluation. MSM are increasingly being recognised as being at risk in the African epidemic as well, with recent data suggesting that they account for a significant proportion of new infections in northern Africa [21–24].

In Asia, the epidemic has established itself in a more complicated way, involving an overlap of *i.v.* drug use and sex work. In Thailand, sex workers were originally identified as a major

source of transmission, and authoritarian programmes focusing on HIV testing, registration and 100% condom use were implemented, with great public acclaim from the government when HIV incidence appeared to decrease. However, the epidemic in the region is very complex, with increasing *i.v.* drug use (see below) and the rise of a large transgender community within the region, often using *i.v.* drugs and engaging in sex work. This group again represents a highly marginalised community with complex health and psychological needs, and with a very high risk of HIV. Paradoxically, as opposed to the difficulty of addressing the generalised large-scale epidemics in Africa and the significant but complex MSM community in other parts of the world, this group is relatively easily identified with public health programmes, and interventions addressing protection, including pre-exposure prophylaxis, should be easier to implement [8, 25].

Recently, data have accumulated showing that lowering plasma viral load profoundly decreases sexual transmission. This correlation has been known to be true for needle-stick injuries and MTCT. At an individual level, this protection against sexual transmission appears to be complete if antiretrovirals have rendered the viral load undetectable. New studies are currently underway investigating discordant couples not using barrier protection but where the positive partner is on antiretrovirals. Observational studies looking at “community viral load”, where all viral loads are averaged and measured against new incident infections, seems to correlate with new infections. Several studies in widely different contexts, including in rural South Africa, have demonstrated decreases in new incident infections with increasing antiretroviral coverage and lowered viral loads. Protection offered by suppressive antiretrovirals has led to this being a formal recommendation and a major public health reason for implementing treatment at higher CD4⁺ count initiation thresholds [26–28].

MTCT and children born with HIV reaching adulthood

Transmission from pregnant HIV-positive women to the unborn fetus and from HIV-positive women *via* breast milk is relatively efficient, with up to one-third of babies eventually contracting HIV in the absence of ART. In generalised heterosexual epidemics, this was a large problem prior to the advent of widespread ART, with HIV-positive children creating a significant and complex stress on health systems, with huge social consequences. Widespread historic programmes that encouraged breastfeeding and complex breastfeeding cultural practices within health systems and communities made it a challenge to discourage breastfeeding, especially in poorer communities where the benefits of breastfeeding on child morbidity and mortality were high. Complex associated cultural behaviours, such as pooling of breast milk in “milk kitchens” or surrogate breast feeding, can further challenge programmes [29, 30].

Prevention of MTCT was one of the first dramatic clinical successes of ART, reporting lowering of transmission with relatively short courses or even a single dose of certain antiretrovirals. Subsequently, many studies have demonstrated that the more suppressive the antiretroviral regimen the less transmission occurs, both during birth and then during the breastfeeding phase. Current recommendations are that the mother gets completely suppressive ART and that this continues beyond breastfeeding, providing maximum protection and cutting the transmission rate to $\leq 2\%$ if initiated prior to conception. Seroconversion during pregnancy, which remains common in generalised epidemics and where the transmission rate is very high, may ensure that HIV-positive babies are seen during the era of ART, and highlight the necessity for repeat testing towards the end of pregnancy [30, 31].

As ART is effective in arresting and reversing the clinical progression of HIV in children as well as adults, more HIV-positive teenagers are reaching adulthood and starting to have their own children. In particular, adolescents pose a complex challenge; in addition to the usual complex adolescent social behaviours, which often manifest in risk taking, they may also have issues related to HIV, including dealing with a sexually transmitted illness while entering their sexual debut. Stunting may occur if the diagnosis is delayed, which may compound the behavioural problems. Adherence, as with other chronic diseases, is a challenge in adolescents and may lead to further behavioural issues, including sexual risk taking, again with public health consequences [32].

Iatrogenic transmission of HIV

Iatrogenic spread has gradually become rarer due to safer international blood screening practices and needle practices. Iatrogenic transmission is unusual, except possibly in poorly functioning health systems, due to current understanding of the importance of only using sterile needles, WHO endorsement of single syringe practices and the wide availability of safe post-exposure prophylaxis after occupational exposure [33].

Haemophiliac populations were among those worst affected by contaminated blood, as pooled plasma relied on the donation of large numbers of units of blood. Due to high-profile blood screening scandals in China, where the number of unverified transfusions related to corrupt practices around blood availability and contaminated equipment was probably in the hundreds of thousands in the 1990s, and in France, where the agency responsible for blood safety knowingly distributed blood contaminated with HIV in the 1980s, much attention and funding have been directed at improving screening for HIV and other blood-borne organisms, in particular the hepatitis viruses. Currently, contaminated blood products are an extremely rare way to contract HIV outside of very poor developing countries, where screening processes are not robust [34, 35].

Occupational post-exposure prophylaxis is very effective. An increased awareness of needle safety, re-engineering of needle design and the move to improve occupational health conditions for staff doing invasive clinical work, have meant that this form of transmission has also become rare.

Intravenous drug use

The sharing of needles during *i.v.* drug use is a significant risk factor for HIV transmission. The illegal nature of recreational *i.v.* drug use has made addressing this group complicated, although places like the Netherlands have had significant success in reducing transmission rates through legal reforms, clean needle exchange programmes, support packages that include safe injecting venues, and the provision of methadone. In places like Canada and certain countries in Europe, these programmes have led to the majority of people with HIV and sharing needles having good adherence to ART, and may have led to the decrease in HIV in *i.v.* drug users in these populations [25, 36, 37].

In Russia, large parts of Asia and Argentina, the majority of new infections are among drug users. In Russia, authoritarian legal approaches, the continued classification of methadone as illegal, and almost no prevention programmes in this group has led to a rapid increase in HIV among the growing number of heroin users in the country. The recent political events in the

Ukraine, which had a relatively successful *i.v.* drug use programme, has meant that many programmes have been stopped in Russian-controlled areas, with probable increases projected in these troubled areas [38].

Pre-exposure prophylaxis is a promising approach to augmenting prevention programmes. Unfortunately, a study performed in Thailand showing that pre-exposure prophylaxis halves the risk of HIV in *i.v.* drug users was hindered by politics and accusations of coercion, as well as poor study design, leading to recent calls for caution in the introduction of the technology [39].

Renewed focus on *i.v.* drug users has been seen with the rise of highly effective treatments for hepatitis C, which is a major problem among drug users. The treatment, which often cures hepatitis C, relies on relatively short periods of treatment that demand adherence. The expense of the treatment coupled with pressure to expand it to these groups due to the significant morbidity attached to hepatitis C, may mean that HIV-prevention programmes among *i.v.* drug users will benefit due to co-screening and linkage to care through adequately integrated programmes [40].

The future

Internationally, the number of new HIV infections is decreasing, but there is huge geographical disparity from the exploding epidemic in *i.v.* drug users in Russia to the new rises in MSM communities. In some countries, it appears, from intense programmes aimed at easily recognised groups such as *i.v.* drug users and MSM, that new infections can be successfully averted. The fear that ART would extend life and hence prolong the infectious period appears to be unfounded. The profound decrease in infection that ART induces far outweighs the modest contributions that prolonged life expectancy confers. There remain fears that people may start treatment too late to realise the prevention benefit, and other concerns that there may be a rise in community ART resistance associated with more indiscriminate and widespread use of the drugs. However, the impact on decreasing the gains made with expanded care will need to be demonstrated. A far greater threat is the possibility of interruptions in ART provision if donor support is decreased. Most countries in Africa, Asia and elsewhere are almost completely dependent on donors for these programmes and, while the cost of ART has decreased dramatically in the past 10 years, even at these levels, they are unaffordable to the poorly financed health systems that exist in these countries. In addition, ART programmes often rely on intermittent and weak drug and clinical supply lines, especially in the most affected countries. Sustainable solutions to these problems are a challenge for international public health, as they rely on individual countries increasing their economies, allocating appropriate health resources out of the national fiscus and ensuring the improvement of their health system occurs, none of which are easy [1, 2, 41].

The fact that the epidemic, even in generalised epidemics, seems to have disproportionate effects in certain groups such as *i.v.* drug users, MSM, transgender people, sex workers and others, raises a paradox. Often these groups are relatively easily identifiable by public health practitioners, and often self-identify as being at risk for HIV, making provision of preventative and treatment services much easier, if resources are available. However, often the legal framework and police harassment make access difficult or impossible. In large parts of Africa, homosexuality is illegal and being identified as such carries a high risk of violence towards them. Sex work is illegal around the world and *i.v.* drug user programmes that are empathic are present in a small minority of the countries that need them. Tackling the complex web of human rights, law and health service provision makes the future of HIV prevention in these

groups extremely challenging [42, 43]. Children will continue to be born with HIV and will require specialised levels of care and medication. Adolescents with HIV will similarly need nuanced and sensitive services.

The future of more conventional prevention interventions, such as both preventative and therapeutic vaccines, or even a cure is difficult to predict. Large amounts of research funding have been invested in the basic sciences surrounding an HIV vaccine, and despite understanding emanating from the basic immunology, the field is scattered with candidate preventative vaccines that failed or may even have increased susceptibility to HIV infection. New generations of vaccines being tested, but will probably only be partially effective. In addition, mathematical modelling suggests that the time between vaccine discovery, manufacture, mass application and public health impact may take well over a decade [44].

In the meantime, HIV control will probably rely on tailored interventions based on understanding of local epidemiology. Conventional programmes in generalised epidemics will continue to rely on condom use and education programmes, with medical male circumcision and increasingly widely available ART adding to community protection. More niche programmes tackling sex workers, *i.v.* drug users and MSM will have local impact if focused correctly.

HIV continues to challenge public health planners, with the complex interplay of science, medicine and politics. The scale and changing nature of the epidemiology will ensure that medical staff, patients and societies will need to be able to deal with the consequences for the rest of our life.

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Current antiretroviral therapy

Alex P. Salam and Anton L. Pozniak

No other area of medicine has progressed as rapidly as HIV. It has now become a chronic disease with on-therapy life expectancies approximating normal. However, there are still important questions that remain unanswered. For example, should all patients start treatment regardless of their CD4⁺ T-cell count? Are there long term toxicities of therapy? And can patients effectively adhere to lifelong treatment? There is a number of combinations of drugs available for effective therapy that are recommended by international guidelines based on clinical trial data of efficacy and safety. Many of the older drugs have unfavourable side-effect profiles and are currently only used in the developing world, where they are being phased out. Drug–drug interactions with both over-the-counter and prescribed medicines, especially with ritonavir, are a major concern, and physicians and patients have to remain alert to these. International guidelines are helpful in distilling and summarising data but, increasingly, choices are based on tolerability and ease of use, and there is still an important role for the individualisation of therapy.

The discovery of HIV as the causative agent of AIDS in 1983 [1, 2] subsequently led to the search for drugs with anti-HIV activity. Zidovudine, a nucleoside analogue, was the first agent found to inhibit HIV replication. The US Food and Drug Administration approved zidovudine in 1987 after a randomised, placebo-controlled trial demonstrated an early reduction in mortality and risk of opportunistic infections in AIDS patients treated with this agent [3]. Although monotherapy with zidovudine was shown to slow the decline of CD4⁺ cell counts in HIV patients without AIDS, it had no effect on disease progression or mortality in this subgroup of patients with early HIV disease [4, 5].

Shortly thereafter, other nucleoside analogues, such as didanosine and zalcitabine, were developed and approved for use. A major breakthrough in treatment came about when dual therapy with two nucleoside analogues was shown to be superior to monotherapy, with significant reductions in morbidity and mortality [6, 7]. The treatment of HIV was transformed in 1996, however, with the advent of a new class of therapeutic agents, the protease inhibitors, and cART was thus born [8]. Combination therapy with the use of three drugs with at least two different mechanisms of action had a profound effect on viral suppression, progression to AIDS and mortality [9, 10]. In the years following the introduction of cART, mortality and AIDS in HIV-infected persons decreased by approximately 60% [11]. Thereafter, the focus of clinical trials moved away from mortality to the ability to fully suppress plasma HIV RNA. Over the past 20 years, the outcome for HIV patients with access to treatment has dramatically changed, and HIV-infected

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individuals with reliably suppressed viral loads on ART and CD4⁺ counts of at least 500 cells·μL⁻¹ appear to have no difference in mortality compared with the general population [12]. While antiviral agents with new mechanisms of action have been developed over the last decade and the number of agents available has increased dramatically since the 1990s, the principles of cART remain much the same.

Principles of ART

The principal goal of ART is viral suppression, defined as an undetectable serum viral load. This is usually set at less than 50 copies·mL⁻¹ but can vary depending on the assay used. Prolonged suppression of viral replication leads to: 1) improvement in CD4⁺ count and, therefore, immune function; 2) prevention of HIV transmission; and 3) prevention of drug resistance.

HIV genome replication is highly error prone due to HIV's lack of proof-reading function. As a result, the mutation rate is extremely high and every possible point mutation occurs in uncontrolled, wild-type HIV replication multiple times over in the course of a single day [13]. Most of these mutants are not replication-capable and only the fittest viruses predominate. In practice, in untreated HIV, there is not one strain of HIV but, rather, a large population of mixed viruses called quasiespecies. Some of these viruses have mutations that would make them naturally drug resistant [14]. If exposed to a single drug, some of these would be selected for and become the dominant quasiespecies. If then exposed to a second drug, further resistance would develop. Even in the simultaneous presence of two drugs, HIV can develop resistance due to selection for double-mutant variants. For this reason, cART with the use of three drugs is superior to dual or monotherapy in suppressing viral replication. It is not statistically possible to find a variant in patients who have never been treated that is resistant to three drugs used in combination, unless a resistant strain has been transmitted. cART therefore consists of the use of three drugs, a “backbone” and a “base”. The backbone generally consists of two NRTIs, while the base consists of an agent from a different class, traditionally a protease inhibitor or a NNRTI. More recently, integrase strand transfer inhibitors (INSTIs) (raltegravir, elvitegravir and dolutegravir) have been added to the list of recommended bases [15].

It should be noted that three-drug regimens composed of three different classes of drugs offer no benefit over three-drug regimens consisting of two different classes of drugs in therapy-naïve patients [16]. Furthermore, regimens that consist of three drugs of the same class are not recommended due to the emergence of resistant mutants [17]. Finally, the use of four-drug regimes in therapy-naïve patients offers no benefit in terms of viral suppression, mortality or morbidity, and is associated with a higher incidence of adverse events [18].

Because HIV integrates its genome into the human genome and forms a latent (*i.e.* dormant) pool of infection, drug combinations have to be taken daily to avoid concentrations falling below the trough concentration and, thus, HIV virions being produced from the latent reservoir.

Drug resistance testing should be performed before the initiation of therapy since transmission of resistant strains between individuals can occur. There are certain situations where one should not wait for the results of resistance testing before initiation of cART, however, such as in the context of opportunistic infections or severe seroconversion illness. The most common resistant strains in treatment-naïve patients are viruses with mutations

that confer complete resistance to the NNRTIs efavirenz and nevirapine (e.g. K103N mutation). Therefore, in the absence of available resistance results, the base generally consists of a protease inhibitor.

Current population sequencing for drug resistance testing can miss drug-resistant HIV variants that exist at low concentrations. However, these can be detected by novel techniques such as deep sequencing [19].

The decision to start cART will be influenced by a number of factors including: 1) the presence of drug-resistant virus; 2) patient comorbidities; 3) interactions with non-HIV drugs; 4) drug side-effect profiles; 5) patient characteristics, including, age, lifestyle and pregnancy status; 6) viral load at baseline; and 7) patient choice. While the decision when to start cART in certain patient subgroups is open to debate, there is unanimous consensus that once cART is initiated, ART should be continued for life due to the risk of viral rebound if interrupted, with consequent decline in immune function and adverse consequences [20]. Although the pharmacokinetics of some combinations are such that occasional missed doses will have little impact on viral suppression, it is imperative that patients are counselled that all doses of antiretroviral drugs should be taken every day. Indeed, one of the most important reasons for failure of ART to suppress HIV replication fully is poor adherence [21].

When to start ART

The decision when to start cART has undergone a number of changes since its introduction. When cART became available in the mid-1990s, the approach was to start all patients on cART as early as possible. However, drug toxicities, pill burden, poor adherence, and thus the emergence of drug resistance and virological failure resulted in clinicians increasingly withholding ART in patients with preserved CD4⁺ counts and immune function. As the number of available antiretroviral agents has increased, and side-effect profiles and pill burden have improved, there is now a shift toward starting cART earlier in the course of HIV again. The CD4⁺ threshold at which initiation of cART is recommended has increased steadily over the years, from <200 cells·μL⁻¹, to <350 cells·μL⁻¹, to <500 cells·μL⁻¹, to all patients with HIV irrespective of CD4⁺ count, depending on which guidelines are followed.

There exists, however, disagreement between different organisations and consensus groups as to when is the exact optimal time to start cART. Currently, the US Department of Health and Human Services (HHS) recommends starting cART in all patients irrespective of CD4⁺ count [15], whereas the World Health Organization (WHO) recommends initiation of cART in patients with a CD4⁺ count of 500 cells·μL⁻¹ or less [22], and the European AIDS Clinical Society (EACS) recommends initiation of cART in patients with a CD4⁺ count of 350 cells·μL⁻¹ or less [23]. There exists a clear and significant mortality and morbidity benefit for initiating cART in patients with CD4⁺ counts <350 cells·μL⁻¹ [9, 24–27], and there appears to be a mortality and morbidity benefit in initiating cART in those with CD4⁺ counts above 350 cells·μL⁻¹ [28, 29], although there is ongoing debate with regards to this. The currently ongoing Strategic Timing of Antiretroviral Treatment trial is examining if there is a benefit to starting at CD4⁺ counts >500 cells·μL⁻¹ (registered at <http://www.clinicaltrials.gov> with identifier number NCT00867048).

The arguments for and against therapy irrespective of CD4⁺ count are summarised in [table 1](#). The principle argument for the initiation of cART in all patients, including those with a CD4⁺ count >500 cells·μL⁻¹, is the hypothesis that there are long-term consequences of ongoing

Table 1. Arguments for and against the initiation of cART in all patients, including those with a CD4⁺ count >500 cells·μL⁻¹

For	Against
Modern regimes have improved drug toxicity	Unknowns regarding long-term drug toxicity
Improved adherence due to simplified regimens and better tolerability	Unknowns regarding the long-term emergence of drug resistance
Highly effective and potent	Cost of ART
Improved CD4 ⁺ count recovery	Unknown how clinically relevant this is in the long term
Uncontrolled HIV leads to chronic inflammation, which exacerbates other comorbidities	Data for this are inconclusive
Reduced HIV transmission	

HIV viral replication in different cell types and tissues, leading to inflammation, which may cause the development and progression of cardiovascular, renal and neurological disease and cancers. Another reason to start early is to reduce the transmission of HIV, with consequent public health benefits [28]. The principle argument against the initiation of cART in patients with a CD4⁺ count >350 cells·μL⁻¹ are side-effects and potential toxicity from long-term ART.

Despite disagreements on the timing of cART initiation in general, there is wide agreement that cART should be initiated immediately in patients with certain comorbidities, irrespective of CD4⁺ count. WHO recommends cART in all patients with active TB, HBV co-infection with severe liver disease, all pregnant and breastfeeding women, all children younger than 5 years, and all individuals with HIV in serodiscordant relationships, regardless of CD4⁺ cell count [22]. EACS also recommends initiation of cART in these groups of patients and also in patients with HIV-associated nephropathy, HIV-associated neurocognitive disorder, AIDS-defining malignancies (*e.g.* Hodgkin's lymphoma and Kaposi's sarcoma) and human papilloma virus-associated malignancies, irrespective of CD4⁺ count [23]. Historically, the management of HIV therapy patients with such conditions was very challenging due to drug contraindications and drug interactions. However, newer HIV drugs, especially the development of agents with fewer drug interactions (*e.g.* INSTIs), has made therapy in such patients generally simpler.

Patients who present with an AIDS diagnosis should generally be started on cART within 2 weeks of presentation. The one exception to this is cryptococcal meningitis, where the risk of IRIS, with subsequent worsening of the initial disease process with immune recovery, can lead to increased mortality. It is best to delay treatment in such patients for about 6 weeks, taking into account clinical, cerebrospinal fluid and radiological factors [30, 31].

Mechanisms of action of antiretroviral drugs

HIV is a spherical retrovirus, consisting of an outer envelope of host-cell membrane origin, within which are two copies of single-stranded RNA genome, each 9.7 kb long, coding for both structural proteins and enzymes. These RNA strands are enclosed by a conical capsid consisting of the viral p24 protein. Within the capsid are enzymes integral to the development of HIV virions, including reverse transcriptase and integrase. The outer lipid

envelope includes proteins of viral origin, namely gp120 and gp41. The life cycle of HIV consists of the following steps, many of which are targets of antiretroviral agents [32, 33].

HIV initially binds to CD4⁺ T-cells and other immune cells *via* attachment of gp120 on the surface of the HIV virion envelope to CD4 receptors on the surface of CD4⁺ cells. As a result, the envelope undergoes a structural change that exposes further binding domains on gp120. These attach to one of either of two chemokine receptors on the surface of immune cells, namely CCR5 or CXCR4, which then allows gp41 to penetrate the host cell membrane, ultimately resulting in fusion of host cell and virion membranes, and entry of the viral capsid. Inhibition of CCR5 binding is the mode of action of the CCR5 antagonist maraviroc, while the fusion inhibitor enfuvirtide binds to gp41, preventing membrane fusion.

Maraviroc binds to a site within the transmembrane helices of CCR5 that is not the active site for either CCR5 chemokines or the HIV envelope, but to which binding induces a conformational change in the CCR5 receptor that prevents HIV gp120 from attaching. Maraviroc only works in patients who have CCR5-tropic virus, that is virus that uses CCR5 as a coreceptor for binding, rather than CXCR4. Resistance to maraviroc can arise by several mechanisms but primarily by the emergence of virus that uses CXCR4 for entry. A genotypic or phenotypic tropism assay is required prior to the use of maraviroc, as it is not active against CXCR4 or dual-tropic viruses.

Following entry of the viral capsid containing RNA, proteins and enzymes into the host cell, the viral enzyme reverse transcriptase copies the viral RNA into cDNA. The reverse transcriptase also has DNA polymerase activity, allowing it to create a sense DNA molecule from antisense cDNA. Viral DNA and cDNA then form a double-stranded DNA molecule that is subsequently transported into the cell nucleus. NRTIs and NNRTIs block the action of reverse transcriptase and, thus, the copying of viral RNA into cDNA.

NRTIs are analogues of the host nucleotides needed to synthesise viral DNA and thus compete with host nucleotides for incorporation into the growing viral DNA chain. NRTIs, however, lack the 3' hydroxyl group needed to form the 3',5'-phosphodiester bond between the NRTI and incoming 5'-nucleoside triphosphates, thus resulting in termination of the viral cDNA chain. Chain termination can occur during the synthesis of either viral cDNA or DNA. NRTIs require phosphorylation by cellular kinases to their triphosphate forms before becoming active. NRTI resistance is mediated through one of two main mechanisms, either: mutations in the polymerase domain of reverse transcriptase that prevent the incorporation of NRTIs into the DNA chain; or mutations in the reverse transcriptase that result in removal of the drug from the replicating chain by pyrophosphorolysis, and thus reversal of chain termination.

Different NRTIs have different genetic barriers to resistance. The genetic barrier to resistance of a drug signifies the number of mutations needed to significantly reduce the susceptibility to that drug. A low genetic barrier signifies that only one or few mutations are needed to result in marked reductions in susceptibility, while the converse applies to a high genetic barrier to resistance. Many NRTI mutations, however, lead to reduced reverse transcriptase function and thus decrease HIV's ability to replicate.

NNRTIs bind to a secondary allosteric site on the viral reverse transcriptase, inducing a conformational change in the reverse transcriptase that reduces the ability of host nucleotides to bind to the reverse transcriptase active site, inhibiting DNA polymerisation and thus slowing viral replication. Mutations that confer resistance to NNRTIs decrease the binding of

the NNRTI to the secondary allosteric site by either changing the overall conformation of the drug binding site or through the loss of important sites involved in binding of the drug. NNRTI mutations generally lead to high level resistance (*i.e.* NNRTIs have a lower genetic barrier to resistance) with minimal reduction in viral fitness. For this reason, such mutations are slow to reverse. As a result, NNRTI mutations are the most frequent and most stable mutations in the population, even in the absence of NNRTI drugs. Most NNRTI mutations result in cross resistance to other NNRTIs.

The double-stranded viral DNA is then transported into the cell nucleus, where it undergoes permanent integration into the host chromosomal genome by the viral enzyme integrase. Integrase catalyses several key events required for integration, including: 1) integrase combines with the viral DNA to form the pre-integration complex (PIC); 2) integrase catalyses endonucleolytic processing of the 3' ends of the viral DNA, exposing reactive hydroxyl groups; and 3) the PIC then enters the cell nucleus, where integrase makes a nick in each nuclear DNA strand, allowing for joining of the viral and host DNA (strand transfer). INSTIs, such as raltegravir and dolutegravir, specifically inhibit strand transfer and block integration of the HIV DNA into the host chromosomal DNA. They achieve this by binding to the active site on integrase that binds to viral DNA. Resistance to INSTIs is conferred *via* mutations in amino acids that coordinate several magnesium cofactors that are necessary for the binding of the INSTI to the integrase active site. Such mutations generally confer resistance to different integrase inhibitors but result in decreased viral fitness. INSTIs generally have a low genetic barrier to resistance but the newest in the class, dolutegravir, appears to be more resilient.

Following integration into the host genome, viral DNA either undergoes immediate or deferred transcription by host RNA polymerase into viral mRNA. When exactly this occurs depends on the activity at the host chromosomal location at which the viral DNA was integrated. Viral mRNA is then translated into polyprotein precursors and HIV protease. HIV protease cleaves these polyprotein precursors into individual protein components, which ultimately assemble, together with viral RNA, at the inner leaflet of the host cell membrane to form whole virions. Protease inhibitors competitively inhibit the HIV protease, inhibiting the cleavage of the polyprotein precursors into their individual components by binding to the active site of protease. The emergence of protease inhibitor resistance requires the accumulation of multiple mutations. Each protease inhibitor usually selects for a characteristic pattern of mutations involving mutations at the primary active site of the protease and/or mutations at various accessory cleavage sites. These mutations are often subsequently accompanied by mutations at other sites that repair the loss of function (and thus replicative fitness) as a result of the primary mutations. Because protease inhibitor mutations often involve a series of mutational steps involving primary and secondary mutations, protease inhibitors have a high genetic barrier to resistance and transmitted drug resistance is rare in protease inhibitor-naïve individuals. For this reason, protease inhibitors are often the base drug of choice in therapy-naïve patients who require immediate treatment and for whom drug susceptibility testing results are not yet available.

The different antiretroviral agents available within the different classes are listed in [table 2](#).

Pharmacology of antiretroviral drugs

Current cART recommended by HHS, WHO and EACS is based on improved toxicity profiles, potency and dosing regimens associated with newer agents compared with many

Table 2. Antiretroviral agents

NRTIs
Tenofovir [#] , emtricitabine [#] , lamivudine [#] , abacavir [#] , zidovudine, didanosine, stavudine, zalcitabine
NNRTIs
Efavirenz [#] , rilpivirine [#] , etravirine, nevirapine
Protease inhibitors
Atazanavir [#] , darunavir [#] , tipranavir, fosamprenavir, lopinavir, saquinavir, ritonavir
Integrase strand transfer inhibitors
Raltegravir [#] , elvitegravir [#] , dolutegravir [#]
Entry inhibitors
Maraviroc, enfuvirtide

[#]: commonly used for HIV-naïve patients.

older ones. As a result, only the pharmacology of currently recommended and routinely used antiretroviral drugs will be discussed in any detail in this section.

Nucleoside reverse transcriptase inhibitors

NRTIs include tenofovir, emtricitabine, lamivudine, abacavir, zidovudine, didanosine, stavudine and zalcitabine.

Most NRTIs have short plasma half-lives, except emtricitabine (10 h) and tenofovir (17 h). Depending on the plasma half-life, NRTIs are dosed either once or twice daily. Many NRTI are eliminated renally and require dose adjustment in patients with impaired kidney function.

The older NRTI side-effects were mainly as a result of mitochondrial toxicity due to their affinity for mitochondrial DNA polymerase. Common and important side-effects of drugs such as didanosine and stavudine included lactic acidosis, lipodystrophy, hepatic steatosis, peripheral neuropathy and pancreatitis. Newer NRTIs (tenofovir, emtricitabine, lamivudine and abacavir) have lower mitochondrial toxicity than older NRTIs and so have generally fewer side-effects. Some side-effects are drug specific, such as renal and bone effects for tenofovir, and hypersensitivity for abacavir, for example.

NRTIs generally have few significant drug–drug interactions because they are not substrates, inhibitors or inducers of hepatic cytochrome P450 (CYP) enzymes, which are responsible for the metabolism of the majority of drugs used in medicine. A comprehensive guide to antiretroviral drug interactions is available at <http://www.hiv-druginteractions.org>.

Abacavir is metabolised by alcohol dehydrogenase and glucuronyl transferase. As such, it generally avoids Child–Pugh score C liver disease. The major issue with abacavir is the risk of a hypersensitivity reaction. Hypersensitivity usually appears within 6 weeks of starting, and symptoms include fever, rash, and constitutional, gastrointestinal and respiratory symptoms. Abacavir should be immediately discontinued if hypersensitivity develops, as the reaction can be fatal. Patients should not be re-challenged with abacavir due to the risk of anaphylaxis. The presence of the HLA-B*5701 allele is associated with an increased risk of developing hypersensitivity [34]. Thus, all patients are screened for HLA-B*5701 before initiation of abacavir. Although some studies have reported an increased incidence of cardiovascular disease in patients taking abacavir, the evidence is conflicting [35, 36].

Lamivudine and emtricitabine are both dideoxycytidine analogues, and structurally very similar. As a result, they cannot be used in combination as a NRTI backbone, as they compete for intracellular phosphorylation. Lamivudine and emtricitabine are primarily renally excreted unchanged. Dose adjustments are therefore required in patients with creatinine clearance (CrCl) $<50 \text{ mL}\cdot\text{min}^{-1}$. Emtricitabine has a mean plasma half-life of approximately 10 h, while the half-life of lamivudine is 6 h. Both drugs have a very low incidence of side-effects, with hair loss, neuropathy and pancreatitis being rare, but the most serious side-effects associated with lamivudine, whilst emtricitabine can also cause hyperpigmentation on the palms and/or soles.

Tenofovir is renally excreted and requires dose adjustment in patients with CrCl $<50 \text{ mL}\cdot\text{min}^{-1}$. The long-term safety of tenofovir in patients with CrCl $<50 \text{ mL}\cdot\text{min}^{-1}$ is unknown. Rarely, tenofovir can cause Fanconi's syndrome (raised serum creatinine, glycosuria, hypophosphataemia and acute tubular necrosis). Patients on tenofovir should have renal function, urinalysis for glucose and protein, and electrolytes monitored regularly. A decline of glomerular filtration rate may occur and, if severe enough, should prompt discontinuation of the drug. Concurrent nephrotoxic therapy, especially high-dose nonsteroidal anti-inflammatory agent use, should generally be avoided. Tenofovir use has been associated with decreased bone mineral density, and bone density should be monitored in patients with other risk factors for bone loss. Tenofovir is a weak inhibitor of CYP1A2 and induces permeability (P)-glycoprotein. It decreases plasma atazanavir concentrations significantly and should therefore only be administered with atazanavir in combination with the booster ritonavir.

Non-nucleoside reverse transcriptase inhibitors

NNRTIs include efavirenz, rilpivirine, etravirine and nevirapine.

NNRTIs have very long serum half-lives compared with most NRTIs. This is clinically relevant when an NNRTI-containing regime is discontinued. If all drugs in a regimen containing two NRTIs and one NNRTI are stopped at the same time, levels of the NRTIs are likely to fall more rapidly than levels of the NNRTI, leaving a period of functional NNRTI monotherapy that may be sufficient to select NNRTI-resistant virus. Some clinicians therefore continue the NRTI backbone for between 3 and 7 days when an NNRTI regimen is stopped. Alternatively, a boosted protease inhibitor can be given in place of the NNRTI for 1 week prior to discontinuing the nucleoside backbone.

The use of more than one NNRTI in cART is contraindicated due to drug interactions, increased side-effects and cross resistance. Many NNRTIs have CYP-inducing activity and, thus, have significant drug interactions. One should consult <http://www.hiv-druginteractions.org> before the initiation of NNRTIs or when commencing a patient on new drugs.

Efavirenz is metabolised by CYP3A4 and CYP2B6, and induces its own metabolism. The inactive metabolites are excreted mostly in faeces, but also in urine to a lesser extent. No dose adjustment is recommended in renal impairment or in mild hepatic impairment. Although the manufacturer recommends not using in severe hepatic impairment, its use in this situation has not been studied.

Efavirenz can cause central nervous system (CNS) side-effects, including sleep disturbances, vivid and unpleasant dreams, a hung-over feeling, agitation, paranoia, depression, mania,

suicidal ideation and depersonalisation, amongst others. These generally resolve within 2–4 weeks although they can persist long term in up to 5% of patients. Patients should be counselled regarding CNS side-effects. High-fat meals increase the peak plasma levels of efavirenz, and efavirenz should therefore be taken on an empty stomach to minimise CNS side-effects. Efavirenz can cause a mild-to-moderate maculopapular rash, which usually resolves spontaneously. Efavirenz is teratogenic in animal studies and some guidelines suggest avoiding it in pregnancy, particularly in the first trimester.

Efavirenz is a moderate inducer of CYP3A4 and CYP2B6; a moderate inhibitor of CYP3A4, CYP2C19 and CYP2C9; and a major CYP2B6 and CYP3A4 substrate. As a result, it has a number of significant drug interactions.

Rilpivirine is metabolised by CYP3A4. It is primarily excreted in faeces unchanged. No specific dose adjustments are recommended in renal or hepatic impairment. Its absorption is increased with food by up to 40% so it should be taken at meal times. Rilpivirine should not be used in patients with a viral load $>100\,000$ copies·mL⁻¹ due to a higher risk of virological failure [37, 38].

The most common adverse drug reactions to rilpivirine include depression, insomnia, headache and rash. Rilpivirine can cause QT interval prolongation, so concomitant use with other drugs that prolong the QT interval should be avoided. As rilpivirine is a major substrate of CYP3A4, co-administration is contraindicated with several drugs.

Protease inhibitors

Protease inhibitors include atazanavir, darunavir, tipranavir, fosamprenavir, lopinavir, saquinavir, nelfinavir and ritonavir.

Significant differences in absorption, half-lives and routes of metabolism exist among the protease inhibitors. Of all the classes of antiretroviral agents, protease inhibitors are the most complex in terms of pharmacokinetics and drug interactions. Newer protease inhibitors, such as atazanavir and darunavir, have more favourable toxicity profiles and lower pill burdens than older protease inhibitors.

The oral bioavailability of protease inhibitors is generally low due to metabolism by the CYP system and, to a degree, cellular efflux by P-glycoprotein. Pharmacoenhancement with low-dose ritonavir significantly increases the bioavailability of protease inhibitors by inhibition of CYPs and efflux transporters. Ritonavir itself is a potent protease inhibitor but has significant side-effects when used as a protease inhibitor alone. The use of subtherapeutic ritonavir (generally 100 mg once daily) as a “boosting” agent increases the drug levels of many protease inhibitors, including the currently recommended atazanavir and darunavir. This enables less frequent dosing and results in improved viral suppression.

Class-wide side-effects of protease inhibitors include hepatotoxicity, hypersensitivity events, lipid abnormalities, lipodystrophy and insulin resistance. Protease inhibitors have extensive drug interactions, including some that are life threatening. Most of these are due to the use of low-dose ritonavir. Low-dose ritonavir for example can interact with numerous medications including macrolides, rifampicin, steroids including steroid inhalers and intra-articular injections, statins, antihypertensives, and various anticancer chemotherapeutic agents. Ritonavir can substantially increase the systemic levels of inhaled fluticasone propionate,

for example, and Cushing's syndrome has resulted from starting patients on steroid inhalers in the presence of protease inhibitor therapy [39]. Beclometasone or budesonide should be used instead as they have a less significant interaction. One should always consult <http://www.hiv-druginteractions.org> before the initiation of protease inhibitors or when commencing a patient on new drugs. Care also needs to be taken with over-the-counter medications and patients should be counselled to check with their HIV physician when starting any new over-the-counter medications.

Atazanavir is metabolised *via* multiple CYP pathways, including CYP3A4. It is mostly excreted in faeces. Atazanavir is generally dosed at 300 mg once daily in combination with 100 mg ritonavir. Ritonavir-boosted atazanavir achieves better trough serum levels. Atazanavir should be administered with food and requires an acidic gastric pH for absorption. Concomitant use of proton pump inhibitors (PPIs) and H2-antagonists is therefore generally contraindicated. If needed, PPIs or H2-antagonists should be administered 12 h after atazanavir. No dosage adjustment is required in renal impairment. Studies have shown low atazanavir levels in haemodialysis patients. Thus, their use in haemodialysis patients is generally not recommended. Atazanavir/ritonavir is not recommended in patients with Child–Pugh score C liver disease.

Atazanavir inhibits UDP glucuronyl transferase (UGT)1A1, which can result in unconjugated hyperbilirubinaemia. About 50% patients on atazanavir will have raised bilirubin levels, of whom around 10% will be jaundiced. If hyperbilirubinaemia is accompanied by significant elevations in liver enzymes, then alternative aetiologies for hyperbilirubinaemia should be considered. Atazanavir can also cause crystal deposition, and gallstones and kidney stones. Many clinically significant drug interactions exist with atazanavir, including with other antiretroviral agents.

Darunavir has activity against wild-type HIV and a range of resistant strains. Darunavir is metabolised by the CYP system, particularly CYP3A4. It is mostly excreted in faeces. It is often dosed at 800 mg once daily in combination with ritonavir 100 mg once daily in treatment-naïve patients. No specific dose adjustment is required in renal impairment. Its use is not recommended in patients with severe liver disease. Bioavailability is increased when taken with food.

Darunavir is a major substrate and strong inhibitor of CYP3A4, and inhibits P-glycoprotein. As with atazanavir, many significant, potentially life-threatening drug interactions exist, mainly related to the use of the concomitant booster ritonavir.

Integrase stand transfer inhibitors

Three INSTIs are currently licensed: raltegravir, elvitegravir and dolutegravir.

Raltegravir is rapidly absorbed and has a terminal serum half-life of 7 to 12 h. Twice-daily dosage of raltegravir is therefore needed to achieve steady and highly inhibitory concentrations. Raltegravir is cleared *via* hepatic glucuronidation and excreted mostly in faeces, but also in urine.

Elvitegravir is metabolised primarily *via* hepatic enzymes, as mentioned, but elvitegravir does not achieve therapeutic concentrations unless administered with the pharmacological booster cobicistat, which has a similar action to ritonavir. Cobicistat inhibits the activity of

the CYP3A and CYP2D6, which are required for elvitegravir metabolism. The half-life of elvitegravir is 13 h, allowing for once daily dosing. The absorption of elvitegravir is enhanced by food, and patients should therefore take it with a meal. Elvitegravir-cobicistat is only available as a single pill co-formulation with tenofovir-emtricitabine (Stribild; Gilead Foster City, CA, USA). Cobicistat inhibits tubular secretion of creatinine, resulting in minor elevations in serum creatinine concentrations, which do not represent a true change in glomerular filtration rate. However, the tenofovir in Stribild can cause true impairments in renal function, and thus any change in serum creatinine should be carefully monitored.

Dolutegravir is primarily metabolised *via* UGT1A1 with a minor CYP3A4 component, and renal elimination of unchanged dolutegravir is <1% of dose. It has a half-life of about 14 h.

Given their primary routes of excretion, neither raltegravir, elvitegravir nor dolutegravir is an issue in renal insufficiency; however, Stribild is contraindicated in patients with marked renal insufficiency.

Serious side-effects are rare with integrase inhibitors. None of the integrase inhibitors are significant substrates, inducers or inhibitors of hepatic CYPs; thus, there are few significant drug–drug interactions. However, elvitegravir is only available as a co-formulation with cobicistat (Stribild), which does have clinically relevant drug interactions.

Antiretroviral drug combinations

The mainstay of cART is two NRTIs and either a NNRTI, protease inhibitor or INSTI. However, there are certain specific combinations of drugs that should be avoided, both in therapy-naïve and therapy-experienced patients, for various reasons. These are listed in [table 3](#). In addition, the following agents are no longer recommended for initiation of therapy in treatment-naïve patients due to toxicity and/or lower potency: stavudine (NRTI),

Table 3. Antiretroviral combinations to avoid

Combinations to avoid	Reason
NRTIs	
Lamivudine and emtricitabine	<i>In vitro/vivo</i> antagonism, same resistance mutation
Didanosine and tenofovir	Rapid selection of resistant mutants
Tenofovir and abacavir	Lack of data on <i>in vitro/vivo</i> antagonism
Zidovudine and stavudine	Synergistic toxicity
Stavudine and didanosine	Toxicity increased <i>e.g.</i> lactic acidosis
NNRTIs	
Efavirenz and nevirapine	Combination less effective than single agents
Protease inhibitors	
Double protease inhibitors	Synergistic toxicity
Combinations	
Nevirapine+tenofovir+emtricitabine (or lamivudine)	Potential lack of efficacy
Unboosted atazanavir+didanosine+emtricitabine (or lamivudine)	Potential lack of efficacy

didanosine (NRTI), nelfinavir (protease inhibitor), indinavir (protease inhibitor) and saquinavir (protease inhibitor). Zidovudine (NRTI) and lopinavir (protease inhibitor) are also rarely used in treatment-naïve patients, and nevirapine and efavirenz are not preferred as first-line NNRTIs. Rilpivirine (NNRTI) should not be used in patients with a baseline viral load $>100\,000$ copies·mL⁻¹ due to the risk emergence of resistance and virological failure [37, 38].

In the AIDS Clinical Trial Group 5202, there was a lower rate of viral suppression and a higher rate of virological failure with abacavir/lamivudine compared with tenofovir-emtricitabine in patients with a baseline HIV RNA level $>100\,000$ copies·mL⁻¹ [40]. For this reason, tenofovir-emtricitabine is generally the recommended NRTI combination in treatment-naïve patients, particularly in those with high-level viraemia.

As a result of clinical trial data, toxicity issues and potency, the following combinations are therefore the main ones recommended for initial therapy in naïve patients by the HHS, WHO and EACS: tenofovir plus emtricitabine (NRTI) or abacavir plus lamivudine (NRTI), and one of efavirenz (NNRTI), rilpivirine (NNRTI) (assuming baseline viral load $<100\,000$ copies·mL⁻¹), darunavir plus ritonavir booster (protease inhibitor), atazanavir plus ritonavir booster (protease inhibitor), raltegravir (INSTI) or elvitegravir (INSTI) plus cobicistat booster (co-formulated with tenofovir plus emtricitabine only).

Conclusion

Unless a cure is found for HIV, patients will need lifelong treatment. This will require low-cost, simple, tolerable and efficacious therapies that have minimal long term side-effects, limited significant drug interactions and a high barrier to resistance. Recently licenced drugs are closer to achieving this ideal profile but there continues to be a need for new drug development.

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Pulmonary immunity

Martin Gnoni and Julio A. Ramirez

Lung immunology is particularly affected in patients with HIV infection. Patients not receiving ART develop immunological and virological failure. In patients with uncontrolled HIV infection, abnormalities of the innate and adaptive lung immunity predispose them to opportunistic infections and opportunistic malignancies. Patients receiving ART have immunological reconstitution, with normal values of CD4⁺ lymphocytes and control of plasma viraemia. In these patients there is persistent chronic lung inflammation and immune activation, which is associated with accelerated pulmonary ageing. COPD and other chronic pulmonary diseases are more common in this population.

The lung immune system constantly interacts with a variety of microorganisms. Even though we have a better understanding of the diversity of microorganisms in contact with the gut mucosa or skin epithelium, the study of the lung microbiome is evolving rapidly. Considering that the alveolar membrane is the largest body surface in contact with the environment, a normal innate and adaptive lung immune system is critical to resolve constant infectious and chemical insults without damaging the pulmonary tissue.

Patients with HIV infection develop global immunodeficiency, which places them at risk for opportunistic infections and opportunistic malignancies. Since the start of the HIV epidemic the lung has been an organ commonly affected by these opportunistic diseases. This may indicate that the immune response in the lung may be disproportionately affected in patients with HIV infection.

During the early days of the HIV/AIDS epidemic, patients had a high burden of PCP, pulmonary TB, bacterial pneumonia and Kaposi's sarcoma of the lung. One study that followed HIV patients from 1988 to 1994 concluded that PCP and bacterial pneumonia were the most common opportunistic infections in HIV patients compared with negative control individuals [1]. These pulmonary opportunistic infections and malignancies are still prevalent in patients who are not receiving ART. Without ART, the majority of patients with HIV develop progressive deterioration of the immune system, with low levels of circulating CD4⁺ cell lymphocytes. This is described as "immunologic failure". Patients also develop a progressive increase in the HIV viral load in peripheral blood, described as "virologic failure". Patients with immunological and virological failure are considered to have uncontrolled HIV infection. The natural history of patients with uncontrolled HIV infection is characterised by the development of AIDS within approximately 10 years and death due to opportunistic infections or malignancies.

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Most patients with HIV receiving ART are able to prevent immunological failure, as well as virological failure. These patients maintain a CD4⁺ T-cell count >350–500 cells·μL⁻¹ and an undetectable HIV viral load in peripheral blood. They are considered to have controlled HIV infection. ART has changed the natural history of HIV infection and most HIV patients with access to therapy achieve durable and, perhaps lifelong, controlled HIV infection with appropriate CD4⁺ T-cell counts and viral suppression. The characteristic pulmonary opportunistic infections or malignancies in patients with uncontrolled HIV infection are rarely seen in patients with controlled HIV taking ART. ART restores lung immunity to the level at which the immune system is able to effectively prevent most opportunistic infections and malignancies. The progression to AIDS, which characterises patients with uncontrolled HIV infection, is also eliminated in patients with controlled HIV infection.

The initial expectation was that HIV infection would become a chronic, well-controlled viral infection and patients with controlled HIV infection would have a natural history similar to individuals without HIV infection. However, despite effective control of HIV replication in plasma and a decrease in overall mortality, there is increasing evidence that HIV patients with controlled HIV infection have a high prevalence of non-AIDS defining respiratory illnesses. Even though ART restores lung immunity, it is clear that a return to normal function is not achieved and the local lung environment accelerates the development of chronic pulmonary diseases. In patients with well-controlled HIV infection, there is an increased incidence of COPD, lung cancer, PH and pulmonary fibrosis when compared with patients without HIV infection. Chronic conditions outside of the respiratory system are also more prevalent in HIV patients with well-controlled disease including cardiovascular disease, neurological disease, metabolic disease, renal disease and liver disease along with different types of solid and haematological cancers [2–5].

From a lung immunology perspective, pulmonary complications in HIV should be evaluated in the context of uncontrolled *versus* controlled HIV infection. The aim of this chapter is to review the topic of lung immunology in HIV infection. To accomplish this we have divided the chapter into: 1) a brief review of lung immunity in the normal host; 2) a description of the primary abnormalities in lung immunity that favour HIV-related opportunistic infections and malignancies in patients with uncontrolled HIV infection; and 3) a description of the primary abnormalities in lung immunity that favour HIV-unrelated chronic lung conditions in patients receiving ART with well-controlled HIV infection.

Pulmonary immunity in the normal host

A multitude of cells of the innate and adaptive lung immune system are present in the alveoli, airways and interstitial tissue. They play a fundamental role in initiating the immune response.

As soon as a microorganism reaches the alveoli, alveolar macrophages recognise the intrusive organism by identification of certain well-conserved, pathogen-associated molecular patterns. This recognition is made by immune receptors called pattern recognition receptors. Some of these pattern recognition receptors are Toll-like receptors (TLRs), a family of receptors characterised by the presence of leucine-rich repeats in the extracellular domain along with an intracellular Toll/IL-1 receptor domain. TLRs are considered to play a critical role in pathogen recognition. To date, around 13 TLRs have been identified [6], with each one being stimulated by a particular type of molecular pattern including lipopolysaccharides (TLR4), lipoteichoic acid and lipoproteins (TLR2), double-stranded viral RNA (TLR3),

single-stranded viral RNA (TLR7 and TLR8), bacterial flagellin (TLR5) and unmethylated CpG DNA (TLR9). TLRs stimulated by fungal recognition patterns include TLR4, TLR2, TLR9, TLR1 and TLR6 [7–9]. Single-stranded RNA that originated from HIV will activate dendritic cells and monocytes *via* TLR 7 and TLR8. Activation of TLRs initiates intracellular signalling that will result in activation of nuclear factor- κ B and the production of several pro-inflammatory cytokines (IL-1, IL-6, IL-12, IL-23 and TNF- α). The development of this local micro-inflammatory environment favours recruitment and activation of more cells from the innate and adaptive immune system. Monocytes reaching the site of inflammation (*via* a CCL2 gradient) become locally activated macrophages. IFN- γ also enhances the expression of the class II major histocompatibility complex, which increases antigen presentation to naïve T-cells [10].

The local secretion of TNF- α , IL-1 β and chemokines by macrophages and dendritic cells facilitates neutrophil vascular adhesion and migration to the site of inflammation. Once neutrophils reach the site of infection they start the clearance of offending microorganisms through the activity of their two types of intrinsic granules (primary or azurophil granules and secondary or specific granules), as well as activation of the respiratory burst using two important enzymes: NADPH oxidase and myeloperoxidase. These processes are necessary to clear the offending pathogens but may also produce considerable tissue damage. In addition to the classic pathogen clearing mechanisms, neutrophils possess a death cell mechanism called NETosis where the release of mitochondrial and nuclear DNA upon antigenic stimulation creates a sticky net with antimicrobial substances on it, such as myeloperoxidase, neutrophil elastase and lactoferrin [11].

When this innate lung immune response fails to control microbial multiplication, clearance of the pathogen relies upon the adaptive lung immune response. This process is initiated by antigen-presenting cells (APCs). The most well-known “professional” APCs are the dendritic cells, which take up antigens and carry them to local lymphoid organs to interact with lymphocytes that have the specific receptor. This migration process is regulated by the local secretion of chemokines such as CCL2, CCL5, CCL20 and CCL21. Not only pulmonary macrophages but also alveolar epithelial cells play a significant role in the local production of chemokines [12, 13].

Even though dendritic cells are considered the professional APCs, other cells such as epithelial cells (specifically alveolar epithelial cells type II) of the respiratory tract and alveolar macrophages can process and present antigens. Once the APCs encounter the specific naïve T-cells they become activated and turn into effector cells with the inflamed organ as the final destination. During this migration process chemokines secreted by local cells (epithelial cells, macrophages and neutrophils) will guide the trafficking of T-cells. The CD4⁺ T-helper (Th) cells are a very important component of the adaptive immunity of the lung. Their proliferation arises as a result of the antigen presentation by APCs through the class II major histocompatibility complex. The CD4⁺ Th cells are divided into Th2, Th1, Th17, T-follicular helper cells and regulatory T-cells which imply different inflammatory and effector cytokine pathways [10].

Th1 cell differentiation is promoted by the action of IL-12 and its main effector cytokine is IFN- γ [10]. IFN- γ further increases the Th1 amplification. IFN- γ receptors are expressed on a range of cells, such as macrophages, dendritic cells, epithelial cells and fibroblasts in the lung, which activate well-defined nuclear transcription factors with the ultimate goal of increasing the secretion of pro-inflammatory cytokines. This pathway is important for the

control of intracellular pathogens such as *Mycobacterium tuberculosis*, listeriosis and salmonellosis. IFN- γ can enhance the macrophage microbicidal capacity in order to clear intracellular pathogens, a process called “classical macrophage activation” (e.g. against *M. tuberculosis*). It also augments the expression of TLRs and nitric oxide synthase with an increase in the local release of ROS, which not only enhances the clearance of microorganisms but also the possibility of tissue damage. It also increases antigen presentation to naïve T-cells through increased expression of the class II major histocompatibility complex on APCs.

Th2 cells produce IL-4, IL-5, IL-13 and IL-10 [10]. These cytokines have been involved in the defence mechanisms against helminthes, with IL-5 being one of the main cytokines involved in eosinophilopoiesis. They also promote B-cell differentiation and antibody responses to T-cell-dependent protein antigens (e.g. immune responses to conjugated vaccines). The IL-4 and IL-13 pathway can lead to “alternative macrophage activation”, which in turn has regulatory effects in order to decrease tissue damage due to an overreaction to helminths.

Th17 cells produce IL-17, IL-21, IL-22 and IL-26 [10]. Their differentiation is promoted by transforming growth factor (TGF)- β and IL-6. T-follicular helper cells help to regulate T-cell-dependent B-cell activation through the secretion of IL-21 and expression of CD40L, and are mainly present in the local lymph nodes. Immune responses that target certain pathogens not only eliminate the offending organism but also create considerable tissue damage (immunopathology). Regulatory T-cells decrease the immunological response and create “tolerance” through the secretion of IL-10 and TGF- β .

Pulmonary immunity in patients with uncontrolled HIV infection

In patients with uncontrolled HIV infection there is a chronic state of immune activation characterised by progressive alterations in patterns of cytokine production. A conceptual framework of lung immunity and associated pulmonary complications in patients with uncontrolled HIV infection is shown in [figure 1](#). Immune activation produces a pattern of chronic inflammation that has been documented at a systemic level as well as at a pulmonary level. Along with the increase in the secretion of pro-inflammatory cytokines (IL-1 β , IL-6, IL-18, TNF- α and IFN- γ) by cells from the immune network, a downregulation of certain cytokines (IL-2 and IL-12) important in the stimulation of the cell-mediated immunity (natural killer cells and cytotoxic T-lymphocytes) is also seen [14, 15]. This is important since these two cytokines are responsible for the clearance of most of the viral infections. Of note, IL-12 is the main cytokine that promotes the Th-1 release of IL-2 and IFN- γ , which in turn increases the cell-mediated immune response. This cell-mediated immune response is essential to control opportunistic infections that are mostly due to reactivation of pathogens, such CMV, toxoplasmosis, *Mycobacterium avium* complex or *M. tuberculosis*. For example, a deficit of IL-12 has been linked to an increased incidence of TB in a cohort of females with HIV [16].

CD4⁺ T-cell dysfunction has been a well-described phenomenon since the start of the pandemic. CD4⁺ T-cell depletion or dysfunction is sufficient to place patients at risk of PCP. There is not only a decrease in the number of cells, they are also dramatically dysfunctional. There is a decrease in the production of IL-2, IL-2 receptor expression and progressive loss of memory and response to mitogens *in vitro* [17]. Paradoxically, these dysfunctional CD4⁺ T-cells show markers of persistent activation, such as CD38, HLA-DR and CD4-CD16. The decrease in the qualitative and quantitative response to antigens predisposes patients to

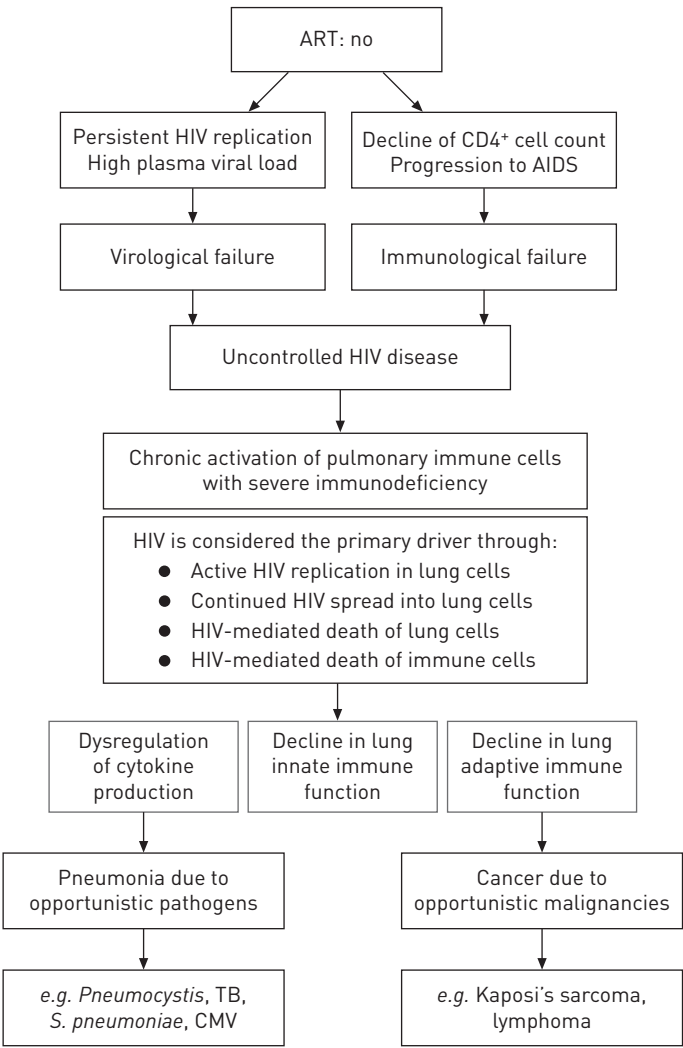


Figure 1. A conceptual framework of the lung immunity and associated pulmonary complications in patients with uncontrolled HIV infection. *S. pneumoniae*: *Streptococcus pneumoniae*.

infections due to reactivation or *de novo* infections. In fact, immune cells in HIV patients show characteristic phenotypic changes compatible with “immune senescence” or “immune exhaustion”, which makes them work inappropriately [3]. Early in the course of the disease, CD8⁺ T-cells also show clear dysfunctional patterns. As long the disease progresses, the CD8⁺ T-cells acquire a phenotype characterised by persistent immune activation with a pattern of immune senescence and immune exhaustion.

B-lymphocytes are also profoundly affected during the course of HIV infection. The response of these cells to antigens is markedly impaired in advanced HIV infection predisposing these hosts to recurrent bacterial infections. After a brief depletion (probably due to redistribution) a polyclonal expansion is almost universally seen. An important proportion of these immunoglobulins are directed against HIV proteins, but overall these B-lymphocytes (that lack the CD21 marker) are not only unable to clear the HIV infection but other bacterial pathogens as well. A proportion of these phenotypically dysfunctional B-lymphocytes recover

some of their functions after starting ART. In clinical practice is not uncommon to find polyclonal hypergammaglobulinaemia in routine laboratory screening tests in HIV patients reflecting the presence of these dysfunctional B-lymphocytes.

Monocytes and macrophages are a well-known reservoir for HIV and both cells suffer profound functional abnormalities that impair the clearance of intracellular organisms, decreasing the effectiveness of the innate immune system against common bacterial and fungal infections. HIV easily infects monocytes and macrophages since they express the CD4 receptor, as well as the co-receptors CCR5, CXCR5 and CCR3. In these cells, HIV produces a non-cytopathic, long-term infection, in an area where antiretroviral drugs are unable to reach [18]. Alveolar macrophages, as well as other tissue macrophages, are clear examples of HIV persistence even in the presence of undetectable viraemia in plasma [19, 20]. One of the most important abnormalities seen is the presentation of antigen by the class II major histocompatibility complex, the process that is crucial for the innate immune system to clear bacterial, fungal and even viral infections (see earlier). Of note, this can also impact on the adaptive immune system (CD4⁺ T-cells) since the immune network is highly interconnected. Macrophages also show a decrease in the secretion of IL-12 and an increase in the production of IL-10 (an anti-inflammatory cytokine), which could, in turn, decrease the local clearance of microorganisms and the recruitment of more professional phagocytes to the site of inflammation.

Natural killer cells are important in the immunosurveillance against viral-infected cells and tumour cells. Innate lymphoid cells are an emerging subset of lymphocytes that are also involved in surveillance against virally infected cells, as well as neoplastic cells. These cells may play an important role in controlling HIV infection and progression. Some of the phenotypic abnormalities shown by this population of cells are the decreased number of CD16⁺/CD56⁺ cells with persistent elevation of markers of immune-activation (similar to what happens with CD4/CD8⁺ T-cells). Alteration of the antibody-dependent cytotoxicity is also observed [21].

Neutrophils are also affected over the course of HIV infection. These cells show markers of persistent immune-activation (like an increase in nitroblue tetrazolium reduction) and patients usually have a decrease in the plasma concentration of antioxidants reflecting an increase in the systemic oxidative stress [22]. There is evidence showing that patients with chronic HIV infection are under chronic oxidative stress [23, 24] along with a state of chronic inflammation and immune activation-dysfunction [25–28]. It has been shown that HIV is also associated with decreased levels of other antioxidants, such as ascorbic acid, tocopherols, selenium, superoxide dismutase and glutathione [23, 29]. The neutrophil opsonising capacity is also impaired and there is an increased rate of spontaneous apoptosis [30].

Pulmonary immunity in patients with controlled HIV infection

The introduction of highly effective ART significantly improved the prognosis of patients with HIV infection. Following a significant decrease in the number of reported cases of PCP and bacterial pneumonia over the years, it became clear that the natural history of HIV was moving towards a chronic disease. It was expected that optimal management of HIV infection would eliminate the state of immune activation and chronic systemic inflammation characteristic of patients with uncontrolled disease. The hope was that patients who were compliant with ART would have a life expectancy comparable to patients without HIV infection. However, ART-mediated immune reconstitution is often incomplete and the levels

of inflammatory markers remain elevated, even in patients who are virologically suppressed. Patients with well-controlled HIV infection have a life expectancy that is below that of the population without HIV infection. Most of the burden of morbidity and mortality regarding pulmonary diseases in well-controlled HIV patients on ART is driven by non-AIDS defining illnesses, such as COPD, PH and different types of lung cancer. A conceptual framework of the lung immunity and associated pulmonary complications in patients with well-controlled HIV infection is shown in [figure 2](#).

The state of chronic systemic inflammation and immune activation that drives immune abnormalities in patients with uncontrolled HIV infection is significantly improved in patients with well-controlled HIV infection, but it is not completely eradicated. Today, it is clear that in patients with well-controlled HIV infection there is persistent low-level immune activation, which damages multiple organ systems. This is considered the primary driver of

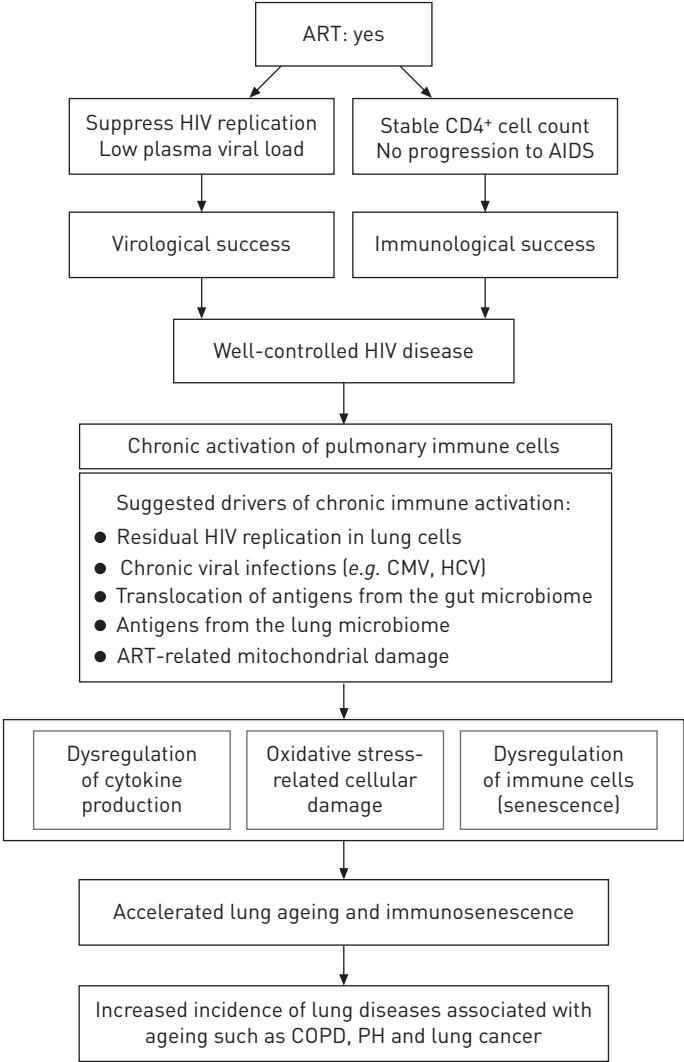


Figure 2. A conceptual framework of the lung immunity and associated pulmonary complications in patients with well-controlled HIV infection.

the increased morbidity and mortality observed in this well-controlled population. These observations have led to the concept of “HIV and ageing” where, even in patients with well-controlled HIV infection, there is accelerated ageing and disseminated organ damage in comparison with matched HIV-negative patients [3–5].

Even though persistent immune activation at the pulmonary level is considered to be the primary driver for a state of chronic lung inflammation, the underlying aetiology and pathophysiology of pulmonary tissue damage is unknown. Recently, the US National Institutes of Health created a consortium to foster research collaborations with the aim of understanding the pathogenesis of lung disorders in patients with well-controlled HIV infection. The University of Louisville (Louisville, KY, USA) is part of this consortium and J.A. Ramirez, in collaboration with J. Roman, is investigating the hypothesis that HIV patients with well-controlled disease have elevated levels of oxidative stress that are mediated by a local exaggerated cystine/cysteine redox potential. Oxidative stress-mediated signalling in lung cells would lead to expression of cellular products with pro-inflammatory and pro-fibrotic effects, such as cytokines and growth factors, matrix glycoproteins and tissue proteases. The persistent and exaggerated production of these factors may activate lung tissue remodelling, thereby promoting HIV-related lung disease in well-controlled HIV patients.

In patients with ART and well-controlled HIV infection, biomarkers of chronic inflammation and immune dysfunction improve but never revert back to their baseline levels. Hence, the immune response to common pathogens is not fully restored [27]. It is now clear that immune activation persists despite suppressive ART and that the ageing process affects not only different organs of the body but also the immune system [26]. As happens with any type of continuous chronic antigenic stimulation, over time this uninterrupted process will result in immune cells that lack effective capability to maintain an adequate immune response to specific antigenic stimuli. As a result, an important number of highly activated immune cells belonging to the innate and adaptive immune system will be circulating not only in the bloodstream but also in different tissues, causing an aberrant and dysfunctional immune response and tissue damage with ineffective clearance of pathogens. In fact, immune cells in well-controlled HIV patients show characteristic phenotypic changes compatible with immune senescence or immune exhaustion which makes them work inappropriately [3, 5]. This may explain why bacterial pneumonia and TB are still frequent in the population of well-controlled HIV patients [31–33]. The Veterans Aging Cohort Study analysed 33 420 and 66 840 HIV-infected and uninfected veterans, respectively, using the International Classification of Disease 9th revision diagnosis. The most common diseases in the HIV group were bacterial pneumonia and COPD [34].

Conclusion

Lung immunity is particularly affected in patients with HIV infection. Patients with no access to care develop significant immunological and viral failure. In patients with uncontrolled HIV infection there are important abnormalities in lung immunity that predispose them to opportunistic infections and opportunistic malignancies (fig. 1).

The development of a therapy for HIV infection that is highly effective, well tolerated and has minimal side-effects has revolutionised HIV management. Patients receiving ART have well-controlled HIV infection with immunological reconstitution and total control of plasma viraemia. However, even in these patients there is persistent chronic inflammation and immune activation. COPD and other chronic pulmonary diseases are more common in this population (fig. 2).

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Vaccines

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Felipe García¹ and José M. Miró¹

Nowadays, in western countries, HIV infection is a chronic disease in patients on effective ART with a life expectancy that is ever closer to that of the general population. However, HIV-infected patients may be at increased risk of infection or experience more severe manifestations following exposure to vaccine-preventable infectious diseases. HIV-infected individuals who travel abroad may require vaccinations against tropical diseases. HIV infection can alter the immune response to vaccination, which varies according to whether patients are receiving effective ART and to the threshold of CD4⁺ T-cell count. The best serological responses have been obtained in patients who are virologically suppressed and with immune reconstitution on ART, although these responses are generally poorer than in HIV-negative patients. For this reason, vaccination guidelines in HIV-infected patients differ from those of the general population: the vaccine doses often need to be higher, the vaccinations more frequent and regular serology testing is necessary to verify the response to vaccines. However, huge efforts are being made to find HIV preventive vaccines in order to prevent new HIV infections and therapeutic vaccines that provide a “functional cure” for those individuals who are already infected.

Immunocompromised patients, and especially patients with HIV infection, may have an increased risk of infection or experience more severe disease following exposure to vaccine-preventable pathogens (e.g. pneumococcal disease) [1]. For this reason, immunisation recommendations may differ from the general population. Moreover, HIV infection, even in patients on cART with controlled virus replication and good immune status, may alter the response to vaccination, and higher and/or more frequent vaccine doses may be necessary for these individuals, as well as more frequent use of serological tests in order to check the response to vaccines [2].

However, the same risk factors for HIV infection facilitate exposure to other vaccine-preventable pathogens, such as HBV [3] or human papilloma virus [4]. An increased risk of exposure to HAV (through oral–anal sexual contact) [5] and invasive meningococcal disease (because of close contact, including sexual contact) [6, 7] has also been described in men who have sex with men (MSM) in metropolitan cities of North America and Western Europe. Furthermore, because of their increased quality of life while on cART, HIV-infected individuals are likely to travel internationally for business or leisure and may require vaccines against typical tropical diseases, such as yellow or typhoid fever [8].

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Finally, although daily cART has led to a good control of HIV infection and has also demonstrated a protective role in prevention of the HIV transmission [9], new infections are still increasing, especially in some categories of patient, such as MSM in western Europe and the USA [10], and daily, expensive treatment is the only option for millions of infected individuals. For these reasons, strenuous efforts are ongoing to find preventive and therapeutic vaccines in order to avoid new infections, to reach the eradication of the virus or, at least, a “functional cure” for individuals who are already infected.

This chapter reviews the general recommendations for immunisation in the adult HIV-infected individual, with a particular emphasis on respiratory infections, and the state of the art of research in preventive and therapeutic vaccines against HIV.

General considerations for immunisation in HIV-infected adults

The immune system’s ability to build a response that will protect the HIV-infected individual after vaccination depends on the individual’s immune status. Humoral and cellular responses are related to patients’ CD4⁺ T-cell counts; other factors such as malnutrition, concomitant active infections and other comorbidities may also have a deleterious effect on the immunogenicity of vaccines.

Vaccine response in HIV-infected patients is compromised [11] because of impaired B- and T-cell function [12–15]. Consequently, the response to vaccines is relatively preserved in the early phase of infection, while is reduced in the advanced phases, especially when CD4⁺ T-cell count drops below 200 cells·μL⁻¹ [1]. Furthermore, given that HIV preferentially infects activated T-cells, activation of antigen-specific T-cells by vaccines favours a selective infection of these cells, with a subsequent alteration in the response to a specific vaccine [12].

Moreover, live vaccines can be harmful, especially for very immunosuppressed individuals, and there are some concerns about the possibility that the administration of vaccines may worsen HIV disease by T-cell activation that leads to an increased HIV replication, which could alter the middle- and long-term course of HIV infection.

Taking into account all these points, we can make some general recommendations for immunisation in HIV-infected patients [1, 2].

- 1) Inactivated vaccines can be administered safely in all HIV-infected individuals.
- 2) As mentioned earlier, humoral and cellular responses are related to patients’ CD4⁺ T-cell counts and response to vaccines may be reduced in people with a low CD4⁺ T-cell count. Despite this, because responses to vaccination can be observed in a substantial proportion of patients with CD4 counts <200 cells·μL⁻¹, the potential benefit of immunisation should not be denied to such persons and it is generally accepted that vaccination in individuals with a CD4⁺ T-cell count below 200 cells·μL⁻¹ should be given, although immunisation must be repeated after immune reconstitution [1].
- 3) Patients with symptomatic HIV infection and/or a CD4⁺ T-cell count below 200 cells·μL⁻¹ must not be given live vaccines. Vaccination with live vaccines may be considered on a risk–benefit basis when immune reconstitution is established and viral replication is controlled. Live vaccines may be administered if CD4⁺ T-cell count is above 200 cells·μL⁻¹.

4) Regardless of the CD4⁺ T-cell count, the use of live vaccines must be avoided in some risk groups, following same rules as for HIV-uninfected patients, such as treatment for malignancies or receiving other immunosuppressive drugs (e.g. methotrexate, cyclophosphamide or cyclosporine) in the previous 6 months or receiving high doses of corticosteroids in the past 3 months.

5) Some authors advise that household and close contacts of severely immunosuppressed individuals should be carefully administered live vaccines [1]. In particular, the Advisory Committee on Immunization Practice advise that they should not be given oral polio and smallpox vaccines, whereas they can receive the measles/mumps/rubella (MMR), varicella, rotavirus [16] and yellow fever vaccines [1].

6) Transient increases in plasma HIV RNA levels and decreases in CD4⁺ T-cell count may be observed a few weeks after the administration of most vaccines. Available evidence indicates that these changes are transient and values return to the set-point thereafter [17]. Physicians should not check plasma viral load (pVL) or CD4⁺ T-cell count for at least 4 weeks after a vaccine's administration.

Vaccines for pulmonary infections

The respiratory tract is recognised to be the site most critically affected as a consequence of HIV infection/AIDS [18]. Although in the initial phase of the epidemic, the lung was involved in almost 100% of cases, currently, in the era of cART, it is involved in some 70% of patients [18]. Pulmonary infections are the major component of these complications, with LRTIs being 25-fold more common than in the general population [19]. Respiratory infections in general remain a major cause of morbidity and mortality and a reason for hospital admission. The spectrum of pathogens causing pulmonary infections in HIV-infected persons is vast, differs in various geographic areas and has changed over the evolution of the epidemic.

In the cART era and after introduction of TMP-SMX prophylaxis, bacterial pneumonia is the most frequent cause of pulmonary infections in HIV-infected patients, followed by PCP and TB [18]. As in the general population, *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia in HIV-infected adults, being implicated in almost 20% of CAP, 40% of cases for which an aetiological diagnosis is made [20] and 70% of cases of bacteraemic pneumonia [21]. *Haemophilus influenzae* is another vaccine-preventable cause of bacterial pneumonia that accounts for 10–15% of cases of bacterial pneumonia with a microbiological diagnosis in HIV-infected patients [18, 20]. Influenza is a common cause of respiratory illness in adults with HIV, although patients on effective cART have a reduced probability of hospital admission [22, 23]. TB is another vaccine-preventable respiratory tract infection and HIV is the most important risk factor for developing TB disease [24]. In the following paragraphs, we are going to describe main aspects of immunisation against respiratory tract infection in HIV-infected adults.

Streptococcus pneumoniae

As mentioned above, the pneumococcus remains a leading cause of serious illness among HIV-infected adults. The incidence of invasive disease is estimated to be 3.8 per 100 000 adults aged 18–34 years in the USA, while for persons infected with HIV, it is as high as 173

per 100 000 [25, 26]. For this reason, most regulatory panels advise that HIV-infected individuals should be vaccinated against pneumococcus [1, 27].

Two different pneumococcal vaccines have been developed: the PPV composed of purified preparations from 23 different serotypes (PPV-23) and the heptavalent PCV (PCV-7). A 13-valent PCV (PCV-13) was approved by the US Food and Drug Administration for use in children and for adults aged >18 years. PCV-13 is identical in formulation for the seven common serotypes in PCV-7 but includes six additional serotypes.

There is conflicting evidence of PPV-23 efficacy in HIV-infected adults. The only randomised clinical trial, conducted in Uganda in patients not receiving cART, failed to demonstrate the efficacy of PPV-23 in preventing all-cause pneumonias [28]. However, a case-control study [29] demonstrated protection against invasive pneumococcal infection, at least in white HIV-infected patients, and other observational studies [30, 31] demonstrated that PPV-23 appears to be protective in patients on cART, although it might be less effective in patients without treatment and low (<200 cells· μL^{-1}) CD4⁺ T cell count [1, 32].

Although clinical trial data are not yet available for evaluation of efficacy of PCV-13 in HIV-infected individuals, a randomised controlled trial in 496 HIV-infected subjects in Malawi [33] concluded that two doses of the PCV-7 vaccine administered 4 weeks apart reached efficacy in preventing recurrent infection of 74% (95% CI 30–90%). Only 13% of these patients were on cART and the proportion of serious adverse events in the 14 days after vaccination was significantly lower in the vaccine arm compared to the placebo arm.

Given the high burden of invasive pneumococcal disease caused by serotypes included in PPV-23 but not in PCV-7 or PCV-13, HIV patients need broader and more effective protection through the administration of both polysaccharide and conjugated vaccines [34]. Outcomes from different studies on sequential use of PPV-23 and PCV-7 in HIV-infected individuals [35–38] are reported in [table 1](#). In general terms, when PPV-23 and PCV-7 were administered in series, a greater immune response was demonstrated when PCV-7 was given first.

Regarding revaccination, most regulatory committees suggest giving a booster dose of PPV-23 vaccine at 5–10 years [1, 27]. However, data on response to revaccination in HIV-infected adults in the cART era are inconsistent because of differences in receipt of cART, duration of cART before revaccination, type of vaccine studied, and dose and sequence of vaccine studied [39–41]. Recently published data [42] suggest that PCV-7 may elicit a better serologic response in HIV-infected adults who had received PPV-23 in the previous 5 years or earlier.

Taking into account all the available data, most regulatory committees recommend that HIV-infected adults who have not received PCV-13 or PPV-23 should receive PCV-13 followed by PPV-23 at least 8 weeks after [27, 34]. A second dose of PPV-23 should be administered 5 years after the first dose. HIV-infected people who have previously received at least one dose of PPV-23 should be given a PCV-13 dose 1 year after the last PPV-23 dose [34]. The UK Department of Health recommends the pneumococcal vaccination to all HIV-infected individuals, independent of immune status [1].

Influenza viruses

Influenza is a common cause of respiratory illness in adults with HIV infection [18], although effective cART seems to reduce the number of patients treated for influenza in hospital [22, 43].

Table 1. Selected studies on antipneumococcal vaccines in HIV-infected adults

First author [ref.]	Intervention	Primary end-point	Study design	Patients n	Immune status %	Median CD4 ⁺ T-cell count cells·µL ⁻¹	cART %	Interpretation/main findings
PPV-23								
BREIMAN [29]	Retrospective comparison of PPV-23 efficacy in preventing IPD	Proportion of IPD	Case-control, retrospective	176 with IPD 327 without IPD	61 64	<200 <200	22 25	PPV-23 demonstrated protection against IPD in Caucasian patients (76% of protection) but not in black patients (24%)
FRENCH [28]	PPV-23 Placebo	First event of IPD	Randomised clinical trial, placebo- controlled	697 695	43 45	<200 <200	0 0	In cART-naïve patients, PPV-23 was not protective [49% efficacy] and all-cause pneumonia proportion was greater in the vaccine arm
RODRIGUEZ- BARRADAS [32]	PPV-23	IgG levels	Case-control	46 HIV on ART (first PPV) 41 HIV on ART (revaccination) 38 HIV off ART (first PPV) 113 HIV 13 healthy controls		352 366 274 504 [#]	100 100 0 100	Immunogenicity better in patients off cART and in patients with CD4 ⁺ T-cell count >200 cells·µL ⁻¹ Better to vaccinate in the earlier phase of infection Immunogenicity in patients on cART is similar to that observed in healthy subjects
FALCÓ [30]	PPV-23	IgG levels	Observational					
PCV-7								
FRENCH [33]	PCV-7 Placebo	Recurrent episode of IPD	Randomised clinical trial, placebo controlled	220 219 (previous IPD)		212 214	14.6 11.9	PCV-7 had a 74% efficacy in preventing recurrence of IPD
PPV-23/PCV-7/ sequential								
FEIKIN [35]	PCV-7 plus PCV-7 PCV-7 plus PPV-23 Placebo plus placebo [interval: 8 weeks]	IgG levels	Randomised clinical trial, open label	18 16 18		378 434 403	87 61 72	Globally, PCV plus PPV arm had better immunogenicity

Table 1. Continued

First author [Ref.]	Intervention	Primary end-point	Study design	Patients n	Immune status %	Median CD4 ⁺ T-cell count cells·μL ⁻¹	cART %	Interpretation/main findings
PEÑARANDA [37]	PCV-7 plus PPV-23 PPV-23 only (interval: 4 weeks)	IgG levels	Randomised clinical trial, open label	110		358	98	No significant differences in immunogenicity except for 23F serotype, favouring prime-boost strategy
				110		351	91	
LESPRIT [36]	PCV-7 plus PPV-23 PPV-23 only (interval: 4 weeks)	IgG levels	Randomised clinical trial, open label	165		351	88	Prime-boost enhances immunogenicity
				103		350	86	
LU [38]	PPV-23 PCV-7	IgG levels	Observational	169		408	100	PCV-7 elicits a better Ab response than PPV-23
				114		403	72	
Revaccination after >5 years from PPV-23								
TASKER [39]	PPV-23 Placebo	IgG levels	Randomised clinical trial, placebo controlled	57 30 with previous PPV-23		274 269	77 90	Limited Ab response with PPV-23 >5-year booster
MIIRO [40]	PPV-23 plus PCV-7 PCV-7	IgG levels	Randomised clinical trial, open label	54 with previous PPV-23 55 with previous placebo		504 453	0 0	Previous vaccination with PPV-23 did not affect Ab response
CRUM-CIANFLONE [41]	PCV-7 PPV-23	IgG levels	Randomised clinical trial, open label	131 73		533 513	84.7 76.7	PCV-7 was only transiently more immunogenic than PPV-23
LU [42]	PPV-23 PCV-7 (one dose) PCV-7 (two doses)	IgG levels	Observational	127 50 44 with previous PPV-23		519 565 479	100 90 90.9	Two doses of PCV-7 for boosting may be more immunogenic than single PCV-7 dose or PPV-23
IPD: invasive pneumococcal disease; Ab: antibody. #: mean CD4 ⁺ T-cell count.								

According to data published in the pre-cART era, HIV-infected individuals were usually considered to be at increased risk of serious influenza-related complications and increased mortality was described during the influenza season [44]. However, more recent studies have demonstrated that HIV-infected patients with pandemic influenza virus A/H1N1 infection who have good viro-immunological control may have a similar clinical outcome to that of non-HIV-infected patients [23, 45].

The influenza vaccine is prepared each year using virus strains or genetic reassortants similar to those considered most likely to be circulating in the forthcoming winter [1]. Several types of vaccine are available for adults (table 2) [46].

Although, in general terms, it is better to avoid live vaccines in HIV-infected individuals, reported data seem to suggest that there is no significant difference in the frequency of adverse events or viral shedding compared with HIV-uninfected individuals receiving a trivalent, live, attenuated influenza vaccine (LAIV) [47, 48]. However, in our opinion, it is better to avoid LAIV in HIV-infected individuals, as valid alternatives are available.

Annual influenza vaccination for adults infected with HIV is recommended by the US Centers for Disease Control and Prevention (CDC) [46], Infectious Diseases Society of America (IDSA) [27] and British HIV Association [1]. A clinical trial published in 1999 [49] showed a 20% absolute reduction in the risk of respiratory symptoms and 100% protection against laboratory-confirmed symptomatic influenza among HIV-infected patients receiving the influenza vaccine compared with those receiving placebo. Although the protective effect is significantly reduced in patients with a CD4⁺ T-cell count <200 cells·µL⁻¹, protection against severe disease is observed in this population compared with unvaccinated persons. Two systematic reviews concluded that influenza vaccination of HIV-infected adults might be effective despite variable antibody responses [50, 51]. However, more data are needed to confirm how effective and safe influenza vaccination is in these patients, particularly among those with very low CD4⁺ T-cell counts [22].

Other vaccine-preventable respiratory infections

Haemophilus influenzae type b (Hib) accounts for 10–15% of bacterial pneumonias with a microbiological diagnosis in HIV-infected patients [18]. HIV is generally considered a risk factor for invasive disease [52], especially in very immunosuppressed individuals [53], bilateral lung infiltrates and a subacute course being more frequent in these patients. Mortality is about 12% in immunosuppressed patients.

However, because the incidence of Hib infections among HIV-infected adults is low [52], Hib vaccine is not recommended for adults with HIV infection without additional risk factors [1, 27, 52].

HIV infection is the most important risk factor for developing TB disease [24]. Additionally, TB is a leading cause of death for people living with HIV in low- and middle-income countries. HIV-infected persons have a substantially greater risk of progressing from latent TB infection to active TB compared with persons without HIV infection [54]. The use of cART has been found to be associated with a notable reduction in the risk of TB but incidence rates remain higher than in the general population [55].

Table 2. Influenza vaccines for adults				
Vaccine	Description	Proprietary name (manufacturer)	Indication	Comments
LAIV4	Quadrivalent, live, attenuated influenza vaccine	Flumist Quadrivalent (MedImmune, Gaithersburg, MD, USA)	Healthy, nonpregnant persons aged 2–49 years	Expected to replace the trivalent formulation
	Quadrivalent, inactivated influenza vaccine	Fluarix Quadrivalent (GlaxoSmithKline, Research Triangle Park, NC, USA)	Persons aged ≥3 years	Will be available in addition to the previous trivalent formulation
ccIV3	Trivalent, cell culture-based, inactivated influenza vaccine	Fluzone Quadrivalent (Sanofi Pasteur, Swiftwater, PA, USA)	Persons aged ≥6 months	Will be available in addition to the previous trivalent formulation
		FluLaval Quadrivalent (ID Biomedical Corporation/GlaxoSmithKline)	Persons aged ≥3 years	Will be available in addition to the previous trivalent formulation
		Flucelvax (Novartis Vaccines and Diagnostics, Cambridge, MA, USA)	Persons aged ≥18 years	
RIV3	Recombinant haemagglutinin vaccine	FluBlok (Protein Sciences, Meriden, CT, USA)	Persons aged 18–49 years Egg-free vaccine, is an option for vaccination of persons with egg allergy of any severity	For persons with egg allergy who have no known history of egg exposure but for whom results suggestive of egg allergy have been obtained on previous allergy testing, consultation with a physician with expertise in the management of allergic conditions is recommended before vaccination [46]
Information from [46].				

The BCG vaccine is a live, attenuated vaccine containing a strain of *Mycobacterium bovis* isolated in 1908 from a cow, which was subcultured 231 times over 13 years, resulting in gradual attenuation. Meta-analyses of published studies have clearly reported that BCG prevents meningeal TB and disseminated forms of TB in children [56, 57]. However, randomised clinical trials have reported estimates of protection against pulmonary TB that vary from nil to 80% [58], and fatal dissemination has been described in immunocompromised individuals. Case reports indicate that symptomatic HIV-infected persons are at greater risk of local ulceration, lymphadenitis, disseminated BCG disease and other complications of the BCG vaccine than HIV-negative persons or persons with asymptomatic HIV infection [59, 60]. These complications can occur several years after BCG vaccination [1]. For these reasons, the BCG vaccine is contraindicated in all patients who are immunocompromised as a result of disease or treatment, including HIV-infected persons, regardless their immune status.

In developed settings, TB is prevented by testing all HIV-infected individuals for latent TB infection; patients with a positive diagnostic test should be treated for latent TB infection if they have neither evidence of active TB nor a prior history of treatment for active or latent TB [61]. The gold standard for treatment of latent TB infection in HIV-infected individuals is daily isoniazid for 9 months [61]. A clinical trial showed that a 12-week course of isoniazid plus rifamycin may be an effective alternative [62].

Hepatitis and other vaccine-preventable diseases

HAV is a Picornavirus transmitted faeco-orally through close personal contact, contaminated food and water, and, rarely, through blood exposure. Person-to-person spread is the most common method of transmission in developed countries. There is evidence that the infection can be spread during sexual contact in homosexual men, and outbreaks of HAV in this group have been described in Europe [63–65], Australia [66], northern America [67] and Japan [68].

HAV infection does not appear to be worse in HIV-infected patients when compared to HIV-negative persons [69], although HAV viraemia may be prolonged [70].

The HAV vaccine contains formaldehyde-inactivated virus grown in human diploid cells. Rates of response in HIV-infected individuals are 50–95% overall but range from 9% at a CD4⁺ T-cell count below 200 cells·μL⁻¹ to 95–100% at a CD4⁺ T-cell count of 300–500 cells·μL⁻¹ [1]. Plasma HIV RNA suppression on cART is associated with improved anti-HAV antibody levels [71, 72]. Increasing the number of doses may also improve response [73]. Duration of protection in HIV-infected people is unknown but may be shorter than in HIV-negative persons [1].

Vaccination is recommended in all HIV-positive persons who belong to a group at risk of the infection or its complications (MSM, injection drug users, and those with hepatitis B or C co-infections) and may be considered in other categories. HIV-infected persons with a CD4⁺ T-cell count >300 cells·μL⁻¹ may follow the standard vaccination schedule and receive two doses at 0 and 6–12 months [1, 27]. The British HIV Association suggests that individuals with a CD4⁺ T-cell count <300 cells·μL⁻¹ should receive three doses over 6–12 months [1]. The combined HAV/HBV vaccine is given at 0, 1 and 6 months. HAV antibodies should be checked at least every 2 years in HIV-infected individuals; if the response is lost, a booster dose should be administered and antibodies titres should be checked at 4 weeks.

HBV is transmitted through sexual intercourse, percutaneous and parenteral exposure to blood and infected body fluids, and vertically from mother to child. Both the risk of HBV infection and that of chronicity are increased in HIV-seropositive persons [3, 74]. Co-infected persons show increased risk of progression to cirrhosis and liver cancer, with a 25–30% lifetime risk of either complication. The mortality rate of HIV/HBV co-infected patients is approximately 10 times higher than that seen in persons with either infection alone [3].

The HBV vaccine is prepared with biosynthetic surface antigen made using recombinant DNA technology. Whereas in immunocompetent recipients, conventional hepatitis B schedules have high immunogenicity (>95% [75]), suboptimal results have been obtained after administration of the standard three 20- μg doses in HIV-positive patients [76]. For this reason, more immunogenic schedules have been attempted in these individuals, including double antigenic load (40 $\mu\text{g}\cdot\text{mL}^{-1}$) [77], using accelerated schedules (0, 4, 8 and 24–48 weeks) [78] and repeating vaccination after a negative result with double (40 $\mu\text{g}\cdot\text{mL}^{-1}$) dose [79]. A better response was demonstrated in a randomised clinical trial for both four intramuscular double doses (40 μg) and four intradermal standard doses, compared with the standard HBV vaccine regimen [80]. Risk factors for a worst response include male sex [81], age >30 years [82], co-infection with HCV [83] and being an MSM [84]. A low CD4^+ T-cell count (<350 $\text{cells}\cdot\mu\text{L}^{-1}$) or rapidly accelerated schedule (20 μg at 0, 7 and 14–21 days, and a booster at 24–48 weeks) were also associated with a poorer response [85].

The 2013 IDSA guidelines suggest vaccinating all nonimmune, HIV-infected adults with the standard three-dose schedule, with consideration of high dose (40 μg) if necessary. If the post-vaccination anti-HBV surface antigen level is lower than 10 $\text{mIU}\cdot\text{mL}^{-1}$, a second three-dose schedule with double-dose HBV vaccine should be administered [27].

Other vaccines' indications do not differ substantially from those for the general population and further details can be found elsewhere [1, 2, 27]. [Table 3](#) shows the recommended routine immunisation schedule for HIV-infected adults.

Immunisation for HIV-infected international travellers

Since quality and quantity of life have substantially improved for HIV-infected individuals on effective cART, there is an increasing demand for international travel (both for business and leisure purposes) among this population [8, 87, 88]. There is also a considerable number of HIV-infected people living in Europe or the USA who are originally from low-income areas that may travel to their own countries to visit friends and relatives. This population is often travelling to rural areas, with increased risk for acquisition of some vaccine-preventable diseases [89]. Recommendations for immunisation in HIV-infected international travel should take into account at least three key points [90]: 1) the nature of the vaccine (live, attenuated, or inactivated); 2) the immune status of the traveller; and 3) the actual risk of vaccine-preventable disease (depending on geographic area, length and type of travel).

Individuals with a CD4^+ T-cell count below 200 $\text{cells}\cdot\mu\text{L}^{-1}$ should not receive live vaccines (including yellow fever, MMR and varicella–zoster) because of the risk of disseminated disease. Alternative inactivated vaccines are available for polio (Salk polio vaccine), cholera (killed cholera vaccine) and typhoid fever (Vi typhoid vaccine), and they should be used in HIV-positive individuals when indicated. However, most live vaccines seem to be safe with higher CD4^+ T-cell counts except for BCG, which is contraindicated for any CD4^+ T-cell count.

Table 3. Schedule for routine immunisation in HIV-infected adults in Western countries

Vaccine	Type of vaccine	Route of administration	Primary course	Booster	CD4 ⁺ T-cell count cells· μ L ⁻¹	Comments
Pneumococcus (PCV-13/PPV-23)	Conjugated/polysaccharide	SC or IM [#]	PCV-13 followed by PPV-23 at least 8 weeks later	PPV-23 at 5 years	Any	Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis [86]
Influenza	Inactivated	IM [#]	Single dose	Repeat yearly	Any	The intranasal live vaccine should be administered with caution in HIV-positive individuals Avoid if possible Adults who have not received Tdap or for whom vaccine status is unknown should receive a dose of Tdap followed by Td booster doses every 10 years thereafter
Tetanus/diphtheria/pertussis (Td/Tdap)	Toxoids (tetanus, diphtheriae)/acellular (pertussis)	IM [#]	Three doses [*]	Every 10 years (Td)	Any	Adults with an unknown or incomplete history of completing a three-dose primary vaccination series with Td-containing vaccines should begin or complete a primary vaccination series including a Tdap dose For unvaccinated adults, administer the first two doses at least 4 weeks apart and the third dose 6 to 12 months after the second [86] Two doses if measles IgG is negative Consider three doses if CD4 ⁺ count <300 cells· μ L ⁻¹ [1]
Measles/mumps/rubella Hepatitis A	Live attenuated Inactivated	Deep SC or IM [#]	Two doses Two doses	None Check Ab response at least every 2 years and administer a booster if necessary	>200 Any	

Table 3. Continued						
Vaccine	Type of vaccine	Route of administration	Primary course	Booster	CD4 ⁺ T-cell count cells·µL ⁻¹	Comments
Hepatitis B	Biosynthetic surface antigen	IM [#]	Three or four doses	Check Ab response at least every 2 years and administer a booster if necessary every 5 years	Any	Consider administering double (40 µg·mL ⁻¹) dose Check anti-HBVsAg 4 weeks after last dose
Quadrivalent human papilloma virus vaccine (HPV-4)	Virus-like particles assembled from recombinant viral coat proteins	IM [#]	Three doses at 0, 1 or 2 and 6 calendar months	No	Any	Males and females aged 11–26 years should receive the vaccine

Td: tetanus/diphtheria vaccine; Tdap: tetanus/diphtheria/pertussis vaccine; SC: subcutaneous; IM: intramuscular; Ab: antibody; HBVsAg: HBV surface antigen.
#: administer subcutaneously in the case of bleeding disorders; ¹: may vary by country and vaccine type.

Vaccines against meningitis (ACYW-135), rabies, Japanese encephalitis and tick-borne encephalitis can be safely administered in HIV-infected individuals.

Patients with impaired immune status may have a lower humoral response to immunisation; this has been demonstrated for HAV, HBV and influenza, among others (see earlier for details). These individuals may be offered HAV immunoglobulin before travel as an additional protective measure.

There are some bacterial and viral infections that are less frequent in Western countries but are highly prevalent in some low-income countries. Meningococcal disease shows a worse course in HIV-infected subjects [91] and vaccination is recommended for travellers to high-risk areas [87], above all to the “meningitis belt” in sub-Saharan Africa during the dry season (January to June), and is mandatory for Hajj and Umrah pilgrims. Measles causes increased morbidity and mortality in HIV-infected individuals [92]. However, the vaccine is not safe in immunosuppressed HIV-infected individuals ($CD4^+$ T-cell count $<200 \text{ cells} \cdot \mu\text{L}^{-1}$) and should be administered on the basis of a careful risk–benefit evaluation. Other infections, such as HAV, HBV, typhoid fever, diphtheria, cholera, Japanese encephalitis, rabies, tick-borne encephalitis and polio, are prevalent in some countries and their administration should be taken into account based on the actual risk of acquisition (*e.g.* travel to rural areas, outbreaks of some diseases during some periods, *etc.*).

Finally, it is worth paying special attention to the yellow fever vaccine, since immunisation is compulsory for travel to most endemic areas of Africa and South America. In our opinion, this live vaccine should be avoided whenever possible in all HIV-infected individuals if the sole reason for administration is admission to a country without an authentic risk of infection, as a definite risk of vaccine-induced encephalitis has not been properly evaluated in people with any $CD4^+$ T-cell count. In this case, a waiver certificate can be released. In the case of an authentic risk of acquisition, the vaccine cannot be administered in immunosuppressed individuals ($CD4^+$ T-cell count $<200 \text{ cells} \cdot \mu\text{L}^{-1}$). Some authors believe that it could be safe in individuals with a $CD4^+$ T-cell count between 200 and $500 \text{ cells} \cdot \mu\text{L}^{-1}$ [1, 87]. However, the CDC advises that those patients may be considered for administration of the yellow fever vaccine but should be closely monitored during the days after the vaccination for evidence of adverse events [93]. For people with a $CD4^+$ T-cell count above $500 \text{ cells} \cdot \mu\text{L}^{-1}$, yellow fever vaccine can be administered if required [93].

Table 4 shows the main vaccines required to travel to tropical areas in HIV-infected individuals.

Research on preventive and therapeutic HIV vaccines

Vaccines have been demonstrated to be the most cost-effective tool to control the dissemination, mortality and morbidity of a number of infectious diseases [94]. The development of effective, either preventive (to avoid the infection) or therapeutic vaccines (to treat already HIV-infected patients) remain the biggest challenge for HIV research in the next years. However, despite the continuous effort to find a vaccine against HIV infection, currently, there are no preventive or therapeutic vaccines effective enough to reach the market. The challenge is huge, and a collaborative model of research (the so-called Global HIV Vaccine Enterprise) has been implemented to increase resources, to prioritise research, to use common standards for the comparative testing of vaccine candidates, to expand resources for manufacturing vaccine candidates and to increase the capacity for the

Table 4. Schedule for immunisation against the main travel-related infections in HIV-infected adults

Vaccine	Type of vaccine	Route of administration	Primary course	Booster	CD4 ⁺ T-cell count cells·µL ⁻¹	Comments
Meningococcus (ACWY)	Conjugated vaccine	SC or IM [#]	Single dose	Every 5 years	Any	Mandatory for Hajj and Umrah pilgrims Strongly recommended for travel to African meningitis belt Only for travellers to endemic rural areas
Japanese Encephalitis	Inactivated	Deep SC	Two doses (0–28 days)	>1 year after primary series	Any	
Rabies (pre-exposure)	Inactivated	IM [#]	Three doses (0, 7, 21 or 28 days)	Post-exposure (0, 3 days)	Any	Vaccine for selective use in long-term travellers to risk areas
Typhoid fever	Capsular polysaccharide vaccine	IM [#]	One dose	Every 2 years	Any	Low threshold to administer vaccine Oral live vaccine is contraindicated in HIV-infected individuals
Tick-borne encephalitis	Inactivated	IM [#]	Two or three doses (depending on vaccine type)	1–3 years (depending on vaccine type)	Any	Selective vaccine for travellers to European and Asian endemic areas
Yellow fever	Live attenuated	SC	Single dose	10 years	<200, contraindicated 200–499, consider if indicated and the risk is high >500, administer if indicated	Only authorised centres can administer yellow fever vaccine Only administer if there is an actual risk of infection

SC: subcutaneous; IM: intramuscular. [#]: administer subcutaneously in the case of bleeding disorders.

development of international clinical trials [95–97]. We will review the current status of research in preventive and therapeutic HIV vaccines, explaining the obstacles for their development, the different strategies used and the next steps for the near future.

Preventive HIV vaccines

Recently, advances in HIV prevention *via* pre-exposure prophylaxis [98–103], topical microbicides [104], male medical circumcision [105], antiretrovirals to prevent mother-to-child transmission [106, 107] and ART in people with HIV to prevent transmission [9] have been reported. Despite these advances, a safe and potent vaccine remains the most powerful tool for the epidemic control of infectious diseases [108]. However, the development of an effective HIV vaccine faces big challenges, including the genetic diversity of HIV, and its high replicative, mutation and recombination capacity, uncertainty about what constitutes protective immunity, and difficulty in the development of antigens that are highly immunogenic. Isolates of HIV have been classified into four groups: M (main), O (outlier), N (new) and P. Each one of these groups is subdivided in subtypes (e.g. group M is subdivided into nine subtypes: A–D, F–H, J and K). Subtypes are genotypic and phenotypic variants of the virus, and the homology between subtypes is estimated to be 60%. In addition to these differences inherent to subtypes, HIV exhibits extremely high replication and mutation rates. A combination of these factors drives not only the emergence of different genetic variants in a population but also genetically different viruses in a single individual. Therefore, an effective vaccine against a viral subtype or strain would not necessarily be protective against others [109]. Another important problem in developing a vaccine against HIV is the extreme difficulty in generating neutralising antibody responses with any vaccine. This is due to a number of causes, such as: 1) high glycosylation of the HIV envelope, where poorly or non-immunogenic glycans prevent antibody access to the underlying peptide structure; 2) the envelope has a variable conformation; and 3) the CD4 binding site is not exposed and this impedes antibodies from accessing this potentially vulnerable site during receptor binding and membrane fusion processes [110]. In addition, an adequate animal model for vaccine research in HIV is not available and the types of immunological responses that are able to control viral replication are not known, although it does seem that the relevance of the different response types changes with the stage of HIV infection. BAROUCH *et al.* [111] published the results of a preventive vaccine in animal models, which suggest that protection against infection is mediated mainly by antibodies against products of the *env* open reading frame, whereas post-infection, control of viral replication is associated with cellular responses against *gag* products. Recent data reported by Picker's group in relation to simian immunodeficiency virus (SIV)-infected rhesus macaques suggest that the induction of effector memory T-cell responses (and not central memory T-cell responses) with a CMV-vectored vaccine is essential for control of viral replication [112, 113].

The development of an effective vaccine requires, on one hand, to select the best targets to attack the virus, and on the other, to find safe candidates to generate broad-spectrum neutralising antibodies and/or to induce HIV-specific cellular responses, mainly in the entry sites (*i.e.* the vaginal and rectal mucosa). A few phase IIb and III clinical trials have tested the effectiveness of these different approaches with modest results (table 5). With the final objective of inducing a potent and protective HIV-specific humoral response, a double-blind, randomised trial of a recombinant HIV-1 envelope glycoprotein subunit (rgp120) vaccine was conducted among MSM and among women at high risk for heterosexual transmission of HIV-1 [114], and another among injection drug users [115]. Despite the successful completion of these efficacy trials and the induction of neutralising antibodies, the vaccine

Table 5. Phase IIb and III preventive vaccine clinical trials testing the effectiveness of different approaches and candidates

First author [ref.]	Volunteers n	Immunogen	Immunogenicity	Efficacy
FLYNN [114]	5403 (5095 men and 308 women)	HIV-1 rgp120	Neutralising antibodies	Vaccine did not prevent HIV-1 acquisition or delay HIV-1 disease progression
PITSITTITHUM [115]	2546 injection drug users	Monovalent subtype B and bivalent subtype B/E (CRF01_AE) rgp120 (AIDSVAX B/E)	Neutralising antibodies	Vaccine did not prevent HIV-1 acquisition or delay HIV-1 disease progression
BUCHBINDER [116]	3000 HIV-1-seronegative participants	MRK adenovirus-5 HIV-1 gag/pol/nef vaccine	Cell-mediated immune responses	Vaccine did not prevent HIV-1 infection or reduce early viral level
HAMMER [117]	2504 men or transgender women who have sex with men	DNA prime (expressing clade B Gag, Pol, and Nef and Env proteins from clades A, B,C) Recombinant adenovirus type 5 boost (expressing clade B Gag–Pol fusion protein and Env glycoproteins from clades A, B, C)	Cell-mediated immune responses	Vaccine did not prevent HIV-1 infection or reduce early viral level
REKRS-NGARM [118]	16 402 subjects	Recombinant canarypox vector vaccine (ALVAC-HIV (vCP1521)) AIDSVAX B/E	Cell-mediated immune responses plus humoral responses	Reduction of the risk of HIV infection in a community-based population with largely heterosexual risk

rgp120: recombinant envelope glycoprotein subunit; CRF: circulating recombinant form; MRK: Merck.

did not prevent HIV-1 infection or delay HIV-1 disease progression. Other clinical trials have used recombinant virus or a prime–boost regimen to induce HIV-specific cellular immune responses. The STEP study was a phase IIb clinical trial testing a serotype 5 adenovirus expressing HIV-1 Gag/Pol/Nef [116], and the HIV Vaccine Trials Network 505 study vaccinated 2504 men or transgender women who have sex with men with a DNA prime (expressing clade B Gag and Pol, and Nef and Env proteins from clades A, B and C) and a recombinant adenovirus type 5 boost (expressing a clade B Gag–Pol fusion protein, and Env glycoproteins from clades A, B, and C) [117]. Both clinical trials failed to demonstrate prevention of HIV-1 infection or reduction of an early pVL set-point. Finally, a combination of a recombinant canarypox vector vaccine (ALVAC-HIV (vCP1521)) (to induce cellular responses) plus a rgp120 vaccine (AIDSVAX B/E) (to induce humoral responses) had an efficacy of 31.2% to prevent HIV acquisition [118]. While this last trial showed only a modest benefit, the results offer insight for future research and have renewed interest in the development of poxviruses as vectors capable of stimulating the cellular and humoral arms of the immune response [119, 120].

Finally, given these disappointing results, it seems clear that new strategies are needed to reach an effective candidate. Some preliminary results in human cohorts, animal models and phase I clinical trials support these new approaches. First, in the last few years, an increasing number of more potent and broader neutralising antibodies in HIV-infected patients have been found [121, 122], and the developmental pathway by which such antibodies are generated and acquire the requisite molecular characteristics for neutralisation have been defined [123]. Second, one of the most promising results has been published by HANSEN *et al.* [112]: approximately 50% of rhesus macaques vaccinated with SIV-protein-expressing rhesus CMV vectors manifest durable, aviraemic control of infection with the highly pathogenic strain SIVmac239. In addition, they showed that regardless of the route of challenge, recombinant human CMV/SIV vector-elicited immune responses control SIVmac239 after demonstrable lymphatic and haematogenous viral dissemination, and that replication-competent SIV persists in several sites for weeks to months [113]. These data provide compelling evidence for progressive clearance of a pathogenic lentiviral infection. Finally, new approaches to rationally design the insert of the different candidates have yielded promising results. HIV-1 mosaic antigens optimised to improve the coverage of HIV-1 diversity [124] or vaccine candidates comprising highly conserved p24 elements have induced robust immunity in animal models [125–127]. Moreover, some of these immunogens were able to alter the hierarchy of epitope recognition in the presence of pre-existing specific responses.

In summary, to find an effective preventive vaccine is one of the biggest challenges in HIV research; new advances in the last few years have opened new ways to advance in this field. As some authors have suggested, the only guarantee of a sustained end to the AIDS pandemic lies in a combination of nonvaccine prevention methods and the development of a safe and effective HIV vaccine [108].

Therapeutic HIV vaccines

The advent of cART has significantly reduced the morbidity and mortality of HIV-1 infection [128]. Despite the clinical efficacy of cART, this treatment by itself is unable to eradicate the infection [129] and to restore an effectively virus-suppressive immune response against HIV [130]. This probably explains the rapid “rebound” of pVL within days or weeks after suspending cART, even after several years of effective therapy [131, 132]. These findings

Table 6. Types of therapeutic vaccines used in clinical trials

First author [ref.]	Immunogen
KAHN [134]	Whole inactivated virus (REMUNE)
GORSE [135]	Recombinant protein (gp120)
POLLARD [136]	Peptide
DORRELL [137]	DNA vectors
PAPAGNO [138]	Recombinant viral vectors
GARCIA [139]	Dendritic cell based vaccines

reinforce the need for suitable long-term treatment. Treatment resistance, adverse effects in the medium-long term and the enormous costs of cART are important limitations for lifelong adherence to this therapy. Although the number of HIV-infected patients on treatment in developing countries has steadily increased in the last few years and has led to a decrease of new HIV infections, treatment demands rise. In fact, the number of new infections surpasses the number of new patients on treatment. Economic, social, cultural and political issues impose major obstacles to the implementation of widespread treatment in developing countries. These concerns highlight the urgency with which new therapeutic strategies must be developed and tested.

A functional cure has been proposed as an alternative to “cART for life” [133]. The concept of functional cure, defined as control of HIV replication without cART, is based on the observation of a low proportion of HIV-infected patients (referred to as elite controllers) who manage to control HIV replication below detectable levels without abnormalities in CD4⁺ T-cell counts for long periods of time. It has been proposed that strong HIV-specific immune responses in these patients, including CD8⁺ T-cell mediated viral suppression, are responsible for this natural functional cure. The main objective of a therapeutic vaccine would be to induce or augment immune responses against HIV infection using planned exposure to HIV antigens in a strong immunogenic context. The best outcome scenario would be that these responses could control viral replication to an undetectable level. Table 6 shows type of therapeutic vaccines used in clinical trials. Initially, “classical approaches”, such as whole inactivated virus (REMUNE) [134] or rgp120 [135], were tested as therapeutic vaccines [140]. In general, the capacity of these early vaccines, as well as those based on DNA vectors [137], to increase the HIV-specific responses and control pVL were very limited. New approaches have been used in recent years that are based on more innovative vectors, such as recombinant viral vectors or autologous dendritic cells (DCs). Regrettably, although most viral vector vaccines were able to induce HIV-specific immune responses in clinical trials, they showed very limited efficacy to control viral replication [138]. By contrast, DC-based vaccines have yielded the best results in this field [140]. The safety profile has been excellent, with only minor local side-effects reported in some clinical trials. No severe side-effects or induction of autoimmunity have been reported. Our group has recently reported the results of a blinded, placebo-controlled clinical trial that suggest that HIV-1-specific immune responses elicited by therapeutic DC vaccines, made up of DCs pulsed with heat-inactivated, autologous whole virus, could significantly reduce the pVL set-point (mean peak drop in pVL of -1.2 log₁₀ copies per mL) after cART interruption in most chronically HIV-1-infected patients treated in early stages [139]. These findings are some of the best, most solid data demonstrating a benefit of therapeutic vaccination. Although not yet a functional cure, these results support future

studies optimising a therapeutic vaccine to control HIV-1 in infected patients and emphasise the importance of targeting DCs to improve antigen presentation and specific immune response.

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Lung transplantation

Hendrik Suhling, Mark Greer and Jens Gottlieb

In recent years, successful solid organ transplantation in HIV-positive patients has been reported, with early experiences in lung transplantation delivering promising results. Infection rates appear comparable in well-selected patients and drug interactions can be managed with regular immunosuppression monitoring and careful selection of ART. Although increased rejection rates have been reported, outcomes after kidney or liver transplantation are comparable to those of HIV-negative patients.

The first experience of HIV in solid organ transplantation was unintended donor-recipient transmission in 1984 [1]. A 65-year-old female with end-stage kidney disease received a cadaveric renal allograft from a donor who was a drug addict. While HIV was detectable 22 days post-transplant, the recipient remained asymptomatic (without treatment) until the third year, when thrombocytopenia developed. 12 months later, PCP was detected and CD4 cell counts declined. The patient died 5 years after transplantation as a result of B-cell lymphoma and pulmonary embolism [1].

Further reports of donor transmission of HIV have subsequently been described in heart, kidney or liver transplantation [2–5]. However, the published data demonstrated limited survival [1, 5] and organ transplantation from HIV-positive donors was forbidden in the USA in 1988. The lack of effective treatment and poor survival led to the consensus that HIV infection represented a contraindication to solid organ transplantation, with guidelines for preventing HIV transmission being released in 1994 [6]. Subsequent guidelines published in 2006 by the International Society of Heart and Lung transplantation (ISHLT) exclude both HIV-positive patients and HIV-positive organs from transplantation [7].

Although no cure exists for HIV, survival has dramatically improved with modern ART [8]. There has also been an enormous shift in the prevalent comorbidities, with compliant patients demonstrating fewer acute and fatal opportunistic infections or malignancies. Instead, the premature development of chronic progressive diseases, including coronary artery disease, renal insufficiency or noninfectious pulmonary diseases, represents major obstacles to long-term survival [9].

Emphysema and PH have been described as HIV-associated lung diseases and represent a potential indication for lung transplantation [10, 11]. While HIV-associated PH affects 0.5% of patients [10], emphysema is much more common and may reflect higher rates of tobacco use in HIV-positive patients (50–65%) compared to the general US population (19%) [12, 13].

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In parallel to improved survival in HIV patients, lung transplantation has gained increasing acceptance as a viable treatment option for various end-stage lung diseases. The leading indications for lung transplantation are pulmonary fibrosis, cystic fibrosis and emphysema, which account for ~80% of all indications worldwide [14, 15].

Survival following lung transplantation, particularly when compared to other solid organ transplantation, remains disappointing, with a median patient survival of 6.9 years [15]. Primary graft failure and infection remain major early complications, with chronic lung allograft dysfunction representing the main cause of death after the first year [16]. Nevertheless, there have been encouraging reports of successful lung transplantation in HIV-infected patients [17, 18]. However, given the limited data, this remains controversial. The aim of this chapter is to review current data, examine issues under debate and highlight possible pitfalls.

Solid organ transplantation in HIV-positive patients: where are we now?

Liver and kidney transplantation account for the majority of procedures performed in HIV-positive patients. Experience in thoracic transplantation is limited to 13 case reports [19].

Among HIV-positive individuals, high rates of co-infection with hepatitis have been reported, particularly among patients with previous intravenous drug abuse or haemophilia [20]. Liver failure resulting from hepatitis B or C infection remains the leading cause of death in these patients [21]. Despite this and numerous reports of liver transplantation in HIV-positive patients, the indication is not universally accepted. Major counter arguments have focused on possible drug interactions, negative impact on HIV control leading to HIV disease progression and the potential for HCV recurrence [22].

A meta-analysis of 64 studies involving 686 patients reported 1- and 5-year survival rates of 84.5% and 63.8%, respectively, following liver transplantation, which are comparable to HIV-negative recipients [21, 22]. HIV progression at 1 year occurred in 13% of HIV-patients with HCV co-infection. HCV recurrence was observed in 95 (52%) out of 184 patients after a median 2 months [22]. Subsequent reports have concluded that antiretroviral drugs may contribute to toxic liver damage and have nephrotoxic side-effects [23].

Nephrotoxicity and HIV-associated nephropathy predispose patients to chronic renal insufficiency and, inevitably, end-stage renal failure. This appears particularly prevalent among African-American populations [24, 25]. Approximately 1% of patients with end-stage renal disease in the USA are HIV-positive, creating potential demand for kidney transplantation [26]. Recently, a prospective multicentre trial examined the safety and efficacy of donor HIV-negative renal transplantation in 150 HIV-positive recipients [26]. All transplant recipients had well-controlled HIV infection, indicated by $CD4^+$ cell counts $>200 \text{ cells} \cdot \mu\text{L}^{-1}$ and viral loads $<75 \text{ copies} \cdot \text{mL}^{-1}$, in the absence of malignant or opportunistic diseases. Patient and graft survival at 3 years was statistically similar to HIV-negative graft recipients. However, the HIV-positive kidney transplant cohort demonstrated two- to three-fold increases in rejection rates, which appeared to be related to pharmacokinetic interactions between antiretroviral and immunosuppressive drugs. Infections were similarly problematic, with 38% of patients requiring hospitalisation due to infections within the median 1.7-year observation period. As with previous studies in liver transplantation, the authors concluded that kidney transplantation is feasible in HIV-positive

candidates demonstrating acceptable CD4⁺ cell counts, low viral load and absence of AIDS defining disease or malignancy [22, 26].

Comparatively few data exist with regard to thoracic organ transplantation in HIV-positive recipients, the majority of which have focused on heart transplantation. HIV infection is known to worsen cardiac function through various mechanisms, ranging from changes in the vascular endothelium to infections and HIV-associated dilated cardiomyopathies resulting in congestive cardiac failure. ART typically increases cardiovascular risk and independently predisposes patients to cardiac failure [27]. Initial experiences in five heart transplant recipients with unknown pre-existing HIV infection were published in 1990, revealing shortened AIDS-free survival under immunosuppression. In this pre-ART study, the leading cause of death was AIDS [28]. A further report, published in 2001, detailed the clinical course of a known HIV-positive patient who underwent heart transplantation [29]. Although the patient endured six biopsy-proven rejection episodes in the first year under triple immunosuppression therapy, he remained alive and free from opportunistic infections at 2-years follow-up.

Subsequently, URIEL *et al.* [30] retrospectively analysed seven HIV-positive patients following heart transplantation. All patients had undergone heart transplantation due to dilative cardiomyopathy and demonstrated normal CD4⁺ cell counts and undetectable viral loads. Under combined ART and immunosuppression therapy, none of the patients developed an AIDS defining illness and viral loads remained low. Whilst five patients experienced rejection episodes, all remained alive at a median of 5 years post-heart transplantation.

To date, there have only been two reports regarding lung transplantation in HIV-positive recipients [17, 18]. The first described a 45-year-old cystic fibrosis patient who was co-infected with HIV and HBV. The patient was receiving tenofovir and efavirenz, along with lamivudine, and had no history of AIDS-related opportunistic infections or liver disease. Having developed respiratory failure, the patient was comprehensively evaluated and subsequently listed for lung transplantation. In 2007, a lung transplant from a HIV-negative donor followed. The patient received basiliximab induction and was commenced on a regular immunosuppression regime on day 1 (tacrolimus and prednisolone), with ART being withheld for the first 3 days post-lung transplantation. CD4⁺ cell counts dropped from 581 cells·μL⁻¹ to 335 cells·μL⁻¹ after lung transplantation, whilst HIV RNA, CMV DNA and HBV DNA remained negative over the initial 3 months post-lung transplantation. Of note, considerable doses of tacrolimus were required (up to 15 mg·day⁻¹) to maintain sufficient plasma levels (12 ± 2 ng·mL⁻¹) under ART. The patient subsequently developed airway stenosis at 9 months necessitating localised desobliterative laser therapy and silicone stenting. At 24 months follow-up, no severe infections or rejection episodes were reported [17].

In 2014, KERN *et al.* [18] reported on the collective experiences of the University of California (San Francisco, CA, USA) and Houston Methodist Hospital (Houston, TX, USA), where three HIV-positive candidates proceeded to lung transplantation. One was transplanted for HIV-associated PAH and developed chronic allograft dysfunction soon after transplantation following repeated acute rejection episodes. The two remaining patients underwent transplantation due to idiopathic pulmonary fibrosis and remained free from chronic rejection at 3.5 and 1.5 years post-transplantation, respectively. No HIV-attributable opportunistic infections or malignancies were reported and treatment interactions were considered minor [18].

Special challenges of transplantation in HIV-positive patients

The main challenges following solid organ transplantation are similar, albeit much more likely, to those seen in HIV-negative patients and consist of: 1) infectious complications; 2) acute rejection; 3) drug interactions; and 4) post-transplantation malignancies.

Infections

The combination of HIV with mandatory exogenous immunosuppression following transplantation would be expected to increase the cumulative risk of infectious complications when compared to either situation in isolation. Both drug-induced immunosuppression and reduced CD4⁺ cell counts increase susceptibility towards atypical infections, including PCP, and fungal and mycobacterial infections [31].

Infectious complications vary depending on the organ transplanted. Among solid organ transplantations, lung recipients have consistently demonstrated the greatest risk for infectious complications [32]. Respiratory tract infections represent an accepted risk factor for chronic allograft dysfunction [26] and use of prophylactic medication against PCP and CMV is commonplace [33]. Whilst few data on infectious complications in HIV-positive lung recipients exist, data extrapolated from kidney and liver recipients may provide some insight into the added risk. Among HIV-positive kidney recipients, infections tended to occur ≤ 6 months post-transplant (60%), affecting 40% of all graft recipients [26]. In HIV-positive liver recipients, the leading infectious complication was viral hepatitis. Median survival was lowest among hepatitis C co-infected patients, whereas those with hepatitis B co-infection were aided due to the known therapeutic benefit of ART on hepatitis B [34].

A retrospective study of 96 patients with known hepatitis C who proceeded to heart transplantation reported an increased incidence in liver-related deaths when compared with uninfected patients [35, 36]. Current recommendations for hepatitis B and C infection in patients scheduled for heart transplantation appear applicable to lung transplantation. The absence of liver cirrhosis or hepatocellular carcinoma remain of utmost importance. Among HCV positive patients, serology assessing HCV RNA and genotype are recommended. In cases where HCV has cleared, a liver biopsy should be considered to evaluate evidence of hepatic infection and cirrhosis. Active HCV infection should still be considered a contraindication. Evaluation of patients with a history of hepatitis B should include complete hepatitis serology. Chronic HBV-infected patients must be stable with <100 copies·mL⁻¹. Liver biopsy is mandatory to exclude both cirrhosis and portal hypertension.

Acute rejection

Acute rejection is common following lung transplantation, affecting 30% of non-HIV-infected recipients in the first year [15] and was evident in all three HIV-positive lung recipients reported by KERN *et al.* [18].

Whilst both liver and kidney recipients with HIV demonstrated increased acute rejection rates compared to HIV-negative recipients, the impact of HIV on acute rejection rates following lung transplantation remains uncertain [26]. A comparison of 1-year cumulative rejection rates between HIV-positive kidney recipients to pooled patients from the US Scientific Registry of Transplant Recipients showed an increased incidence of 31% *versus* 12.3%, with acute rejection also tending to occur earlier in HIV-positive patients [26]. Whilst

infection represents a known risk factor for rejection, the importance of therapeutic immunosuppressive drug levels in preventing rejection cannot be understated. HIV infection is known to increase T-cell responsiveness and promote nonspecific enhancement of allo-immunity, which itself may influence the onset of rejection [26, 37].

Drug interaction

Identifying appropriate treatment regimens that minimise drug interactions and their inherent toxicities is a major challenge for solid organ transplantation in HIV-positive patients [38]. Traditionally, it was assumed that combination of immunosuppressive medications and ART would create severe, essentially unmanageable, interactions. However, recent experiences appear to allay many of these original fears and have not demonstrated major detrimental effects in HIV-positive solid organ organ recipients [17].

Typical triple-agent immunosuppressive regimens comprising of glucocorticoids, a calcineurin inhibitor and an antimetabolite (e.g. mycophenolate) or proliferation signal inhibitor are used. Most are substrates of hepatic cytochromes (e.g. 3A4) and are therefore influenced by ART drugs (fig. 1). Typical interactions between ART and common immunosuppressive agents are illustrated in table 1. Drug monitoring has previously demonstrated that significantly higher daily doses of tacrolimus are needed in transplant

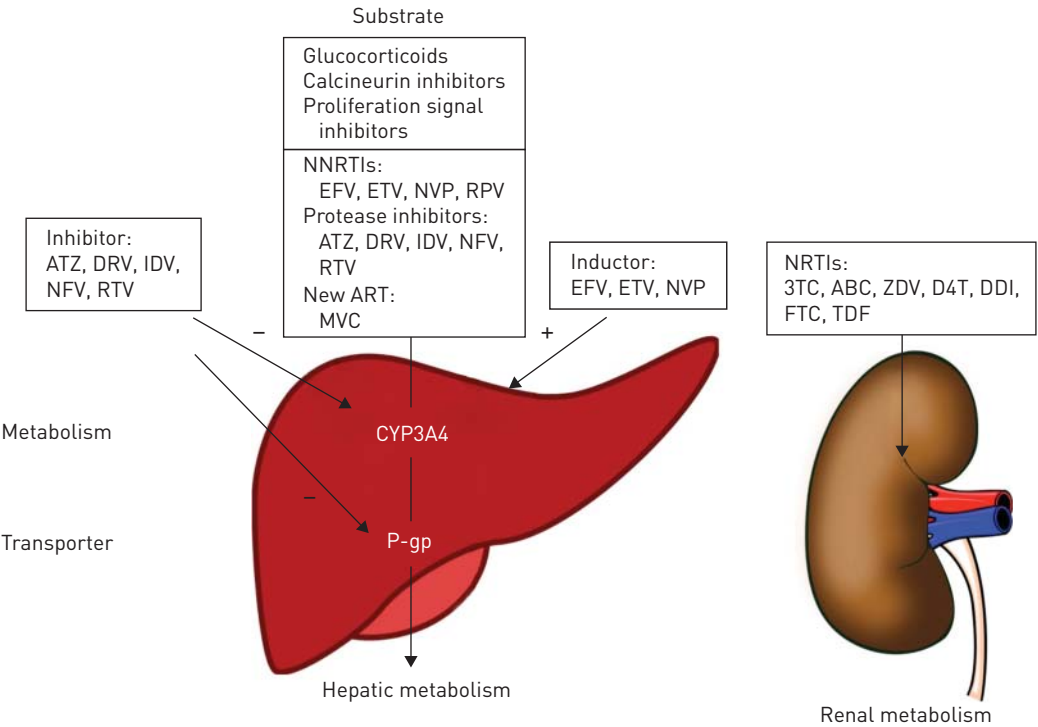


Figure 1. Hepatic and renal metabolism of immunosuppressive and ART drugs. Most immunosuppressive and ART drugs are metabolised by hepatic cytochrome P450 3A (CYP3A4) enzymes and partly eliminated by the transmembrane transporter P-glycoprotein (P-gp). Renal metabolism is less relevant for immuno-suppressive/ART interactions. ATZ: atazanavir; DRV: darunavir; IDV: indinavir; NFV: nelfinavir; RTV: ritonavir; EFV: efavirenz; ETV: etravirine; NVP: nevirapine; RPV: rilpivirine; MVC: maraviroc; 3TC: lamivudine; ABC: abacavir; ZDV: zidovudine; D4T: stavudine; DDI: didanosine; FTC: emtricitabine; TDF: tenofovir.

Table 1. Interactions between immunosuppressive drugs and ART drugs

	ART drugs				
	NRTI (tenofovir [#] , lamivudine)	NNRTI (efavirenz [#] , etravirine)	Protease inhibitors (atazanavir [#] , ritonavir)	Integrase inhibitors (raltegravir [#])	Fusion inhibitors (maraviroc [#] , enfuvirtid)
Immunosuppressive drugs					
Glucocorticosteroids	↔	↓	↔	↔	↔
Calcineurin inhibitors [¶]	↔	↓	↑ ↑	↔	↔
Antimetabolites ⁺	↔	↔	↔	↔	↔
Proliferation signal inhibitors	↔	↓	↑ ↑	↔	↔

[#]: interactions were evaluated using drug interaction software (AID Klinik version 1.9.14; Dosing GmbH, Heidelberg, Germany); [¶]: ciclosporin or tacrolimus; ⁺: mycophenolic acid or azathioprine.
↔: no influence on drug level; ↓: immunosuppressive trough level reduced; ↑: immunosuppressive trough level increased.

recipients requiring ART (tenofovir, efavirenz and lamivudine) [17]. The same authors also reported large fluctuations in serum trough levels and recommended close monitoring.

The use of two NRTIs, *e.g.* tenofovir and lamivudine, in combination with a NNRTI is common, but the latter significantly increases the risk of significant drug interactions. Equivalent outcomes may be achievable in the absence of such drug interactions by substituting the NNRTI with a protease inhibitor [38]. Similarly, the combination of two NRTIs and an integrase inhibitor (*e.g.* raltegravir) should not interact significantly with standard triple therapy immunosuppression [38]. A number of other medications routinely used in managing solid organ transplant recipients have known interactions with ART. These include proton-pump inhibitors, statins and azole antifungals. Alternative therapies should be considered where treatment is necessary.

Post-transplantation malignancies

The risk of post-transplantation malignancy increases steadily in the years following solid organ transplantation. In particular, reduced host anti-viral immunity resulting from immunosuppressive treatment facilitate EBV replication and subsequent transformation of B-cells that may induce a post-transplant lymphoproliferative disorder (PTLD) [39]. EBV-naïve patients exhibit the highest risk for PTLT when in receipt of an EBV-positive organ. Whilst concerns remain with regard to a theoretically increased risk of malignancy and, in particular, PTLT development among HIV-positive organ recipients, no literature is currently available.

Patient selection

Patient selection for lung transplantation is a complex but necessary aspect of improving subsequent patient survival and quality of life [7, 40, 41]. Disease-specific selection criteria for candidates with COPD, PH or fibrosis have been proposed by the ISHLT (table 2) and

Table 2. General requirements and main indications for lung transplantation in HIV-positive patients

	Indications	Absolute contraindications
General requirements	End-stage pulmonary disease with limited life expectancy No alternative therapy Social and psychiatric stability Age <65 years Low quality of life and good motivation	Substance abuse Current smoker Non-adherence Uncontrolled pulmonary infection Significant obesity (BMI ≥ 35 kg·m ⁻²) End-stage coronary heart disease or second organ failure Malignancy with a disease free-period of <2 years
COPD	FEV ₁ <20% predicted Oxygen therapy or NIV Underweight 6MWT <200 m Frequent exacerbations Mean PAP >25 mmHg	
PAH	Functional status of NYHA III–IV Low (<350 m) or declining 6MWT Cardiac index <2 L·min·m ⁻² Right atrial pressure >15 mmHg	
Fibrosis	DLCO <35% predicted or impossible to perform Long-term oxygen therapy $\geq 10\%$ decrease in FVC over 6 months Decrease in pulse oximetry to <89% during 6MWT PH (mean PAP >25 mmHg)	

All patients must comply with general requirements and none of the absolute contraindications are allowed. BMI: body mass index; NIV: noninvasive ventilation; 6MWT: 6-min walk test; PAP: pulmonary artery pressure; NYHA: New York Heart Association; DLCO: diffusing capacity of the lung for carbon monoxide. Data from [10, 42].

will soon be updated [40, 41]. Absolute contraindications for lung transplantation include uncontrolled systemic infection, active malignancy, treatment non-adherence or addictive behaviour including smoking [43]. Adherence is of critical importance, given the discipline required to comply with complicated exact medication regimens, variable dosing, measurement of drug levels and life-long communication with the treating transplant centre [43–45].

General listing criteria for HIV-positive patients have been adapted from existing heart and abdominal transplantation recommendations and are shown in [figure 2](#). Stepwise assessment of a potential candidate should begin with an assessment of current treatment adherence, which is partly reflected by CD4⁺ cell counts and viral load: documented stable disease for at least 3 consecutive months would be considered the lower limit of acceptability. Values reported within kidney transplantation of CD4⁺ cells >200 cells· μL^{-1} and <50 copies·mL⁻¹ (assay dependent) of the HIV viron have been adopted in the current ISHLT recommendations as cut-off values for lung transplantation.

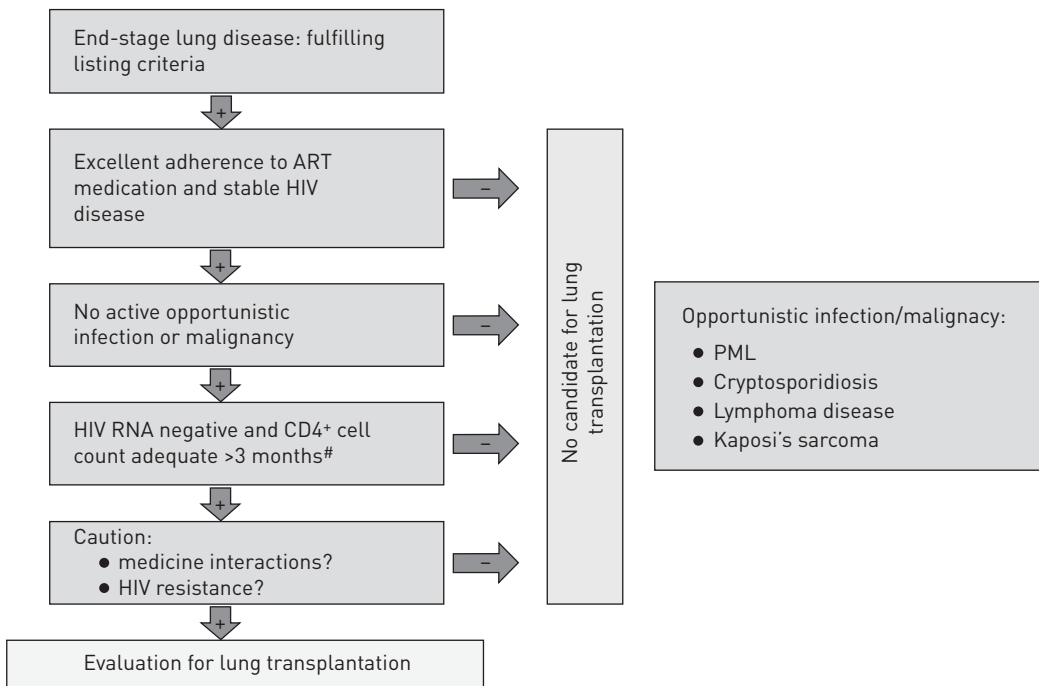


Figure 2. Flowchart of the evaluation process for HIV-positive candidates for lung transplantation. Listing criteria for end-stage lung disease are no different to those in HIV-negative candidates [10]. #: CD4⁺ T-cell counts must be $>200 \text{ cells} \cdot \mu\text{L}^{-1}$ for ≥ 3 months and viral load should be undetectable. PML: progressive multifocal leukoencephalopathy.

HIV-specific infectious complications, such as cryptosporidiosis and John Cunningham virus infection presenting as progressive multifocal leukoencephalopathy, as well as lymphoma or Kaposi's sarcoma, must be actively excluded prior to listing. Other infections, e.g. *Mycobacterium* infection or active hepatitis, should be considered relative contraindications and judged within the overall individual context. HIV-positive candidates should be evaluated in experienced centres utilising interdisciplinary assessment panels with local expertise in managing HIV, as well as transplantation. This facilitates assessment of both general and disease-specific indications for lung transplantation along with the possible contraindications and avoidance of ART-associated drug interactions. This multidisciplinary approach should continue beyond lung transplantation, to provide the best standard of integrated care.

Perspective

These initial case reports of successful lung transplantation in HIV-positive recipients help raise awareness of the possibility of lung transplantation for HIV patients with end-stage lung disease. Additional challenges both in pre-transplantation evaluation and subsequent maintenance therapy post-transplantation in HIV-positive patients are apparent, but the presumed increased risk may not be as high as first thought. Much more information, particularly with regard to long-term sequelae, is needed but short-term results appear promising.

With regard to limited organ availability in many regions, the utility of HIV-positive donors raises interesting ethical questions, but nevertheless should be discussed. In the USA, the

Table 3. Key points

Lung transplantation in HIV-positive patients is possible in selected patients. Short-term graft survival appears acceptable based on current case reports. More data are required to assess long-term outcomes.

Graft acute rejection rates appear increased among HIV-positive liver and kidney recipients, necessitating intensive post-transplantation monitoring.

Intensive drug monitoring appears necessary to prevent significant interactions between immunosuppressants, ART and other co-medications.

Patient selection is paramount, with emphasis on current treatment adherence and their ability to correctly self-manage. Specific assessment of HIV-associated contraindications (malignancies, resistance and infection), as well as virus and CD4 status, are mandatory.

Cooperation between HIV and lung transplantation specialists is essential, both prior to listing and during subsequent post-transplant care.

debate has already begun regarding the use of organs from HIV-positive donors for known HIV-positive recipients. Especially, transmission of drug-resistance of the HIV virus from one patient to another must be excluded before transplantation [46]. How organ evaluation can be performed remains open at the moment; there are no data on whether CD4⁺ cell count or viral load of the donor influences the outcome of an otherwise stable HIV-positive recipient. Consequently, organ evaluation concepts, listing and distribution infrastructure for HIV-positive patients must be established.

Conclusion

Lung transplantation in HIV-positive patients appears possible, with preliminary data suggesting acceptable early graft survival. An increased risk of acute rejection in kidney and liver HIV-positive recipients has been observed and further studies are needed to accurately verify this risk in lung transplantation. Misconceptions regarding concomitant use of ART and established solid organ transplant immunosuppression regimens have been dispelled by recent studies. Questions remain regarding the theoretically increased risk of malignancy among HIV-positive transplant recipients. Pre-transplant evaluation and patient selection represent major challenges in HIV-positive patients. Extra consideration, particularly regarding drug interactions, potential infectious complications and existing treatment compliance, require close and lifelong co-operation with the treating HIV physicians (table 3).

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HIV in pregnancy: diagnostic and therapeutic implications for the newborn

Mark Fredric Cotton¹, Stuart Maxwell Kroon² and Helena Rabie¹

Better uptake and improved interventions to prevent vertical transmission have reduced the incidence of paediatric HIV infection. Early antenatal identification of maternal HIV status is essential to optimise prevention. Late or missed identification and acute HIV in pregnancy and during breastfeeding increase the risk of transmission. Antiretroviral (ARV) prophylaxis should be initiated by 20 weeks' gestation for maximal efficacy. Partner testing must be encouraged. In high prevalence settings, females initially testing negative should be retested later in pregnancy, during labour and while breastfeeding. Infants at increased risk of transmission require PCR testing and multi-ARV post-exposure prophylaxis as soon as possible after birth. Early infant diagnosis by PCR is less sensitive during infant post-exposure prophylaxis and should be repeated twice between 2 and 8 weeks after cessation. Drug resistance genotyping is important to identify vertically transmitted resistant infections. Infant ARVs should be selected on the basis of maternal ARV exposure and resistance testing results. Finally, HIV-exposed uninfected infants are at greater risk of morbidity and mortality than HIV-unexposed infants.

In November 1982, a case of unexplained immunodeficiency and opportunistic infections was reported in four infants from New York, New Jersey and San Francisco, USA [1]. The mothers of these infants had epidemiological risk factors for AIDS and vertical transmission of the causative agent was postulated. This agent, HIV, was identified 5 months later [2].

The global plan for elimination of vertical transmission by 2015 has identified India and 21 countries in sub-Saharan Africa as the source of almost 90% of all new vertical HIV infections [3]. Nevertheless, HIV transmission still occurs in resource-rich countries. For example, at least 167 infants were perinatally infected in the USA in 2010 [4].

This chapter focuses on the implications of HIV in pregnancy for newborn management, testing and treatment. In the absence of intervention, the transmission rate varies between 14% and 30%, depending on maternal health and mode of feeding. High morbidity and mortality in children was noted in the era preceding cART.

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In 1989, LALLEMANT *et al.* [5] drew attention to the extremely high mortality in HIV-exposed infants in Brazzaville, Congo, where by 12 months of age, the probability of survival was 0.61 in HIV-exposed infants *versus* 0.97 in unexposed infants. 15 years later, a meta-analysis of seven African trials for prevention of mother-to-child transmission, with nearly 3500 HIV-exposed children, documented that 52% of HIV-infected children had died by 2 years of age [6]. Preceding prevention of mother-to-child transmission, cART and TMP-SMX prophylaxis, the large ZVITAMBO (Zimbabwe Vitamin A for Mothers and Babies) project conducted between 1997 and 2001 reported that >62% of infants had died by 2 years of age [7].

Routes and timing of vertical HIV transmission: implications for infants

Prior to programmes for prevention of mother-to-child transmission, the risk of transmission was as follows: *in utero* transmission was between 5% and 10%, intrapartum transmission was 10–15% and postpartum transmission was between 5% and 10% [8].

In 1992, BRYSON *et al.* [9] developed a working diagnosis for distinguishing *in utero* infection from intrapartum infection. Virological confirmation of HIV within 48 h of birth was proposed for *in utero* transmission with intrapartum transmission being detectable by virological testing later [9]. *In utero* HIV infection has been described at 12, 15, 16 and 20 weeks' gestation in aborted fetuses [10–13]. However, frequency of *in utero* transmission is more intense closer to term [14]. In the ZVITAMBO project, risks of mortality of infants with *in utero* transmission increased four-fold between 8 weeks and 6 months of age compared to HIV-unexposed infants [7]. A subsequent analysis confirmed that *in utero* infection had a much higher mortality than either intrapartum (positive HIV DNA PCR within 96 h of birth) or early postpartum (negative PCR by 96 h and positive at 6 weeks) [15].

Breast milk transmission of HIV was first documented in 1985 [16] and, in the absence of intervention, can double the HIV transmission rate over 2 years of breastfeeding. In the absence of antiretrovirals (ARVs), transmission is significantly reduced if breastfeeding is exclusive and not mixed with formula milk [17]. Linking HIV transmission to breastfeeding had a negative impact in resource-limited settings. Analysis of studies between 1980 and 1998 showed that breastfeeding substantially reduced mortality, pneumonia and gastroenteritis. Although most protection occurs in the first few months of life, benefit extends into the second year [18].

Prevention of mother-to-child transmission over time

Prevention of mother-to-child transmission has been a great success story. The landmark Paediatric AIDS Clinical Trial Group P076 study was conducted between 1991 and 1993 and reported in 1994. HIV-infected pregnant females between 14 and 34 weeks' gestation with CD4⁺ T-lymphocyte counts >200 cells·μL⁻¹ who were ARV naïve in the current pregnancy were randomised to receive placebo or 100 mg zidovudine (ZDV) five times per day antenatally and intravenously in labour. After birth, the infant received ZDV at 2 mg·kg⁻¹ every 6 h for 6 weeks, beginning 8–12 h after birth. In an interim analysis, 13 (7.2%) out of 180 infants in the ZDV group and 40 (21.9%) out of 183 in the placebo group were HIV infected. This finding was confirmed in a later analysis of a more complete sample of 400 infants [19]. 4 years later, a report limited to ZDV given during labour or postnatally as post-exposure prophylaxis established the importance of these components. The transmission rate

was between 9% and 10% when ZDV was started within 48 h of life and >18% when initiated from day 3 of life [20].

In the developed world, ART, comprising three ARVs from two different classes, became the standard of care in pregnancy in 1998 [21]. By 2006, mother-to-child transmission rates had declined to <2% [22]. In Europe, the transmission rate was <1% between 2001 and 2003 [23]. In well-resourced settings, formula feeding was widely and successfully implemented. However, in resource-limited settings, the benefits of reducing HIV transmission were offset by the disadvantages of formula feeding [24].

In resource-limited settings, trials were undertaken to simplify the ARV regimens and to make breastfeeding safer. These were first reported in 1999. In the first studies from Thailand, also restricted to formula-fed infants, ZDV given every 12 h antenatally and every 3 h orally in labour significantly reduced vertical transmission [25, 26]. In two studies in west Africa, where breastfeeding was the norm and essential for child survival, simplifying ZDV delivery also reduced transmission rate, but less so [27, 28]. These simplified protocols were still difficult to implement in most high-prevalence settings. 6 months after the first of these reports, the landmark HIVNET 012 study showed the efficacy of single dose nevirapine (NVP) for mothers and infants compared to single-dose intrapartum ZDV administered to the mother and twice-daily ZDV administered to the infant for 1 week [29]. This simple regimen facilitated the establishment of prevention of mother-to-child transmission programmes in high-prevalence settings in the public sectors. Of note, rapid tests to detect HIV antibodies became available in 2002, facilitating post-test counselling and initiation of prophylaxis on the day of testing.

Recognising that pregnant females often access healthcare late, LALLEMANT *et al.* [30] systematically studied the duration of prophylaxis necessary for optimal prevention. For mothers initiating ZDV at 28 weeks' gestation, only a short course of ZDV was necessary for the infant, but with shorter antenatal exposure from 35 weeks, a longer postnatal course of ZDV was more effective. Of note, only longer antenatal exposure to ZDV reduced *in utero* transmission [26]. In a subsequent study, giving single dose NVP in labour and to the infant in addition to antenatal, intrapartum and neonatal ZDV substantially reduced transmission to <2% and rapidly became the standard of care [30].

Initially, ART was reserved for females with a CD4 count <250 cells· μL^{-1} or advanced HIV [31]. However, in 2006, the World Health Organization (WHO) recommended that the CD4 threshold in pregnancy be increased to 350 cells· μL^{-1} for stage 3 disease and 200 cells· μL^{-1} for stage 1 and 2 disease. Females not meeting ART criteria were to start ZDV monotherapy from 28 weeks' gestation with single-dose NVP in labour and infant single dose NVP and ZDV for 1 week. When antenatal ZDV was inadequate, infant ZDV was extended to 4 weeks.

A series of studies in Africa confirmed the benefits of maternal ART [32–34] and extended infant NVP [35] for reducing vertical transmission during prolonged breastfeeding.

In November 2009, WHO released “Rapid Advice” [36], followed in 2010 with revised guidelines recommending lifelong ART for pregnant females with CD4 counts <350 cells· μL^{-1} and NVP or ZDV for 4–6 weeks in infant [37].

Two options were advocated for females not requiring ART for their own health, both from early in the second trimester. Option A advocated antenatal ZDV, boosted intrapartum prophylaxis and infant NVP or ZDV for 4–6 weeks. Breastfeeding infants were to take NVP

for the duration of breastfeeding. Increased experience with extending NVP beyond a single dose led to its incorporation in these recommendations [35]. Option B was ART for the duration of pregnancy and until the infant was fully weaned from breastfeeding. The infant then only required 4–6 weeks of NVP or ZDV. Maternal ART provided adequate protection during breastfeeding beyond 6 weeks.

Then, because of programmatic issues such as difficulty in measuring CD4 counts, option B+ was proposed and then formally adopted as an option by WHO. Here, ART was initiated and continued for life in all pregnant females due to its simplicity for implementation [37]. Additional advantages include protection of the infant in subsequent pregnancies and reduced risk of sexual transmission to uninfected partners.

Current guidance in resource-limited settings is exclusive breastfeeding for the first 6 months and, thereafter, the addition of complementary feeds while continuing breastfeeding to 12 months of age. Maternal ART or daily NVP reduces breast milk transmission to the infant to very low levels. Abrupt weaning is no longer recommended [37].

HIV in pregnancy: morbidity and mortality

Maternal HIV is associated with increased maternal and neonatal morbidity and mortality, regardless of the infant's HIV status. In a large retrospective study of >33 000 females in Botswana between 2009 and 2011, HIV status was associated with an increased rate of stillbirth, low birth weight for gestational age, prematurity and neonatal death after adjusting for traditional risk factors such as advanced maternal age, anaemia and hypertension [38]. Poor maternal health or mortality related to HIV is associated with impaired child health, nutrition and survival [39]. Suboptimal management of maternal HIV infection during breastfeeding is likely to be linked to increased rates of postnatal virus transmission [40].

Risks for vertical transmission

High maternal plasma HIV RNA, low CD4 count, maternal malaria and obstetric factors, such as mode of delivery instrumentation and prolonged rupture of membranes, are well-established risk factors for HIV transmission. Prematurity and being small for gestational age are additional risk factors [39, 41]. In high prevalence settings for HIV, co-infection with *Mycobacterium tuberculosis* is also common, contributing to maternal mortality, prematurity, low birth weight and vertical transmission of both HIV [42] and *M. tuberculosis* [43] (table 1).

When antenatal ART or ZDV are started early in pregnancy, transmission rates are extremely low. An important factor is delayed initiation of therapy. For example, in the French perinatal cohort, mothers of infected babies had a median duration of pre-delivery ART of 9.5 weeks compared to 16 weeks for uninfected babies. The mother-to-child transmission rate was 6.6% when delivered before 33 weeks' gestation *versus* 1.2% when delivered after 37 weeks' gestation [44]. In the Women and Infant Transmission Study (WITS), no transmission occurred at <1000 copies·mL⁻¹ [45]. However, a meta-analysis of nine studies reported a 5% transmission rate of <1000 copies·mL⁻¹ in mothers receiving either no treatment or only ZDV monotherapy, therefore suggesting some risk [46]. In analysis from the London HIV Perinatal Research Group, a plasma HIV RNA level <50 copies·mL⁻¹ was compromised if the baseline level was >10 000 copies·mL⁻¹ and ART was started after 20.4 weeks' gestation [47].

Table 1. Risk factors for increased transmission of HIV

Phase	Risk factor	Comment
Maternal	Low CD4	Any detectable plasma HIV RNA has risk Elective caesarean section should be considered Integrase inhibitors reduce viral suppression more rapidly than other ARV classes
	High viral load	
	Short duration of ART	
	Poor adherence	
	Active TB	
Obstetric	Acute HIV infection	Avoid artificial rupture of membranes and fetal blood sampling
	Late diagnosis of HIV	
	Duration of rupture of membranes	
	Instrumentation	
Infant	Fetal blood sampling	
	Prematurity	
Breastfeeding	Delayed initiation of antiretrovirals	
	Acute maternal HIV infection	
	Engorgement during weaning	
	Cracked nipples	
	Mixed feeding	

With close to universal intrapartum and post-exposure prophylaxis, *in utero* infection is now more common than intrapartum transmission. In a study from Johannesburg, South Africa, 29 (76%) out of 38 infections were detectable on day 1 of life in a setting where the prevention of mother-to-child transmission intervention was antenatal ZDV and intrapartum single dose NVP for the mother and single dose NVP and ZDV for the child for 1 week [48]. In a large trial of three post-exposure prophylaxis regimens, of 1684 infants whose mothers had either received no ARVs or only ZDV in labour 5.7% had *in utero* infection and 3.2% acquired infection intrapartum [49]. Intrapartum transmission was reduced to 2.2% and 2.4% in infants receiving two or three ARVs, respectively.

The highest risk of transmission is during acute HIV infection. Antenatally, acute HIV infection has a three-fold increased risk of transmission, with 30% of breastfed infants becoming infected [50–52]. Important strategies to prevent acute maternal infection include counselling on condom use and regular testing in pregnancy, at delivery and during breastfeeding.

Diagnosis of HIV in the mother and infant

As antibodies cross the placenta and may persist up to 18 months of age, detecting HIV-specific antibodies in an infant is a marker of HIV-1 exposure rather than HIV infection. The US Food and Drug Administration approved the first ELISA test to screen for antibodies to HIV in 1985 [53]. Rapid antibody tests, available from 2002, can be performed from a finger prick. If positive, a second specimen is collected and confirmed with an assay from a different manufacturer. These antibody tests, although accurate, will miss the first vital weeks of acute infection. Most rapid tests become positive by 8 weeks following infection and by 12 weeks,

>97% of tests are positive [54]. Rapid tests should now be repeated later on in pregnancy, at delivery and also during breastfeeding to identify initial false-negative tests and seroconversions. Adding p24 antigen to the rapid test did not increase ability to detect acute HIV infection [55]. Delivering this level of testing is challenging and implementation is incomplete. Another strategy for diagnosing acute HIV infection is pooling of maternal samples for HIV RNA PCR from mothers who are antibody negative in pregnancy. In a study from North Carolina (USA), conducted between 2002 and 2005, 15 acute HIV infections, including five from pregnant females, were detected in 187 101 tested samples [56]. In an earlier report, 147 PCR tests were necessary to detect one person with acute HIV using the pooling strategy [57]. In high-prevalence areas, incident HIV infection during pregnancy and breastfeeding substantially contributes to vertical transmission [58].

Partner testing is inadequately implemented and should be encouraged. Identification of infected partners of seronegative females will allow for interventions that reduce incident infection in these females and, in turn, will reduce vertical transmission and infant mortality [59].

HIV-1 diagnosis in infants, apart from recognising the mother's HIV status, depends on demonstrating the presence of the virus. In the past, detecting the p24 antigen was easy to perform but not sensitive. Viral culture was reliable but required specialised laboratories. Detecting HIV-specific nucleic acid through the PCR assay for infant diagnosis was first established in Brazzaville [60]. These tests were approved in 2001 by the US Food and Drug Administration and thus facilitated early infant diagnosis. Within the same month, the first genotypic tests for ARV resistance were also approved [53]. Since then, DNA and RNA PCR tests have been the standard of care for infant diagnosis [61]. A recent exciting development is point-of-care testing for HIV DNA and/or RNA. In a recent pilot study in Mozambique, nurses in primary care clinics successfully diagnosed HIV in 65 (7.9%) out of 827 HIV-exposed infants at a median age of 1.4 months with only two discordant results, compared to a nucleic acid test in the reference laboratory [62]. Point-of-care tests have huge potential to detect acute infection in pregnancy, neonates and infants, thereby facilitating early treatment.

Timing, frequency and sensitivity of diagnostic PCR tests for infants

Either HIV DNA or RNA PCR tests are recommended. Current guidelines for the USA recommend PCR in all HIV-exposed infants at 14–21 days, 1–2 months and then from 4–6 months. Definitive testing should be at least 14–21 days after cessation of post-exposure prophylaxis [63]. In resource-limited settings, a single PCR, usually DNA based, is recommended at 4–6 weeks of age [64]. In practice, it is usually performed at 6 weeks, coinciding with the first immunisation visit.

The reliability of a single PCR at 6 weeks is questionable. In a post-exposure prophylaxis study, 15 (31.9%) out of 47 diagnoses were made after a negative PCR between 4–6 weeks of age [49]. Therefore, the limitations of the PCR assay with increased exposure to ARVs should be considered [63]. ARV exposure may affect sensitivity of the test through reduction of viral replication. In a recent systemic review of studies only using commercial assays for HIV-DNA PCR, sensitivity and specificity were excellent when infant viral load was high [65]. In a French cohort comprising 65 infected and 1502 exposed uninfected infants who received ARVs after birth between 1994 and 2006, plasma HIV-RNA and cellular HIV-DNA PCR were compared. Both tests missed 11% of positive cases at 1 month of age and no cases at

3 months of age [66]. To illustrate this problem, a recent case report from Philadelphia, USA described an infant whose mother was diagnosed late in pregnancy [67]. The infant received two doses of NVP and ZDV, and lamivudine until 5 weeks of age, when post-exposure prophylaxis was discontinued due to neutropenia and anaemia. A qualitative HIV-1 RNA assay was negative at 2 and 5 weeks of age but positive at 6 weeks when it was inadvertently repeated. The confirmatory plasma HIV RNA was high [67]. In a different context, but emphasising the lack of sensitivity of a DNA PCR during ART, GARCIA-PRATS *et al.* [68] described three children in Lesotho, all with confirmed HIV infection by DNA PCR and initiating ART between 2 and 4 months of age. Negative rapid antibody tests and HIV DNA PCRs after 18–20 months on ART prompted ART discontinuation with subsequent viral rebound [68]. Difficulty in confirming HIV infection in infants exposed to single dose NVP has stimulated technical innovations in PCR technology for dried blood spots. Using specimens from Mozambique and sent to Seattle (WA, USA), MITCHELL *et al.* [69] increased sensitivity by 39% by increasing the volume of specimen (extra dried blood spots) and using multiple real time PCRs for different viral products. In practice, testing in the first 48 h of life is difficult, with a small but important number of equivocal results. Retaining mothers and infants in care for confirmatory tests can be challenging.

During breastfeeding and after weaning, it is vital to retest the infant for infection. The cut-off point for loss of maternal antibody is traditionally 18 months of age. In an African setting, antibody decay is more rapid. In a study from KwaZulu-Natal (South Africa), all HIV-exposed uninfected infants had cleared antibodies by 13 months of age [70]. However, antibody reversion may be delayed beyond 18 months after exposure to multi-ARVs for prevention. In a recent study, 14% of 744 infants had antibody persistence until 18 months of age and 1.2% after 24 months of age [71].

Early and very early ART

The Children with HIV Early Antiretroviral trial established the importance of early ART initiation. In infants with a relatively high CD4 count ($\geq 25\%$) and without severe HIV disease at the time, starting ART at a median of 7 weeks of age reduced risk of death by 74% compared to a deferred strategy and created the imperative for early diagnosis and immediate cART worldwide [72]. In a sub-study, children randomised to immediate treatment showed better neurodevelopmental outcomes than those whose treatment was deferred in the first year of life [73]. Of note, the two early ART arms had planned treatment interruption close to the first or second birthday. The long-term outcome was excellent [74]. In a subsequent cohort study, 250 (62%) out of 403 infants already had advanced disease at a median (interquartile range) of 8.4 (7.2–9.7) weeks of age, pointing to major implementation problems outside of a clinical trial setting [75].

The recent report of the Mississippi baby changed the focus of early infant diagnosis and early ART to the first 2 days of life. The mother, presenting in active labour and without antenatal care, was diagnosed as HIV infected by a rapid antibody test [76]. The infant was initiated on ZDV for post-exposure prophylaxis soon after birth. At 31 h of life, in keeping with recommendations for infants with a high risk of transmission, lamivudine and NVP were added [77]. Lamivudine was given at $4 \text{ mg}\cdot\text{kg}^{-1}$ twice daily (double the recommended dose for the first month of life) and NVP at $2 \text{ mg}\cdot\text{kg}^{-1}$ twice daily without a “lead-in” daily dose [78]. Early HIV DNA and RNA PCR tests were positive. After excellent viral control, the infant was lost to follow-up for 6 months. On re-engagement, the infant was in excellent health with only minimal traces of residual viral DNA and RNA on repeated testing, thus

creating the hope that very early intensive ART might, in some cases, permit post-treatment control. However, the infant restarted ART at 45 months of age when plasma HIV RNA was detected at $16\,750\text{ copies}\cdot\text{mL}^{-1}$ and $10\,564\text{ copies}\cdot\text{mL}^{-1}$ 72 h later. The conclusion was that very early ART induced a remission rather than cure but had also reduced the HIV reservoir to extremely low levels [79].

The IMPAACT (International Maternal Paediatric Adolescent AIDS Clinical Trial) network has initiated a multicentre international study to identify infants in whom very early diagnosis and ART might reproduce the outcome of the Mississippi baby [80].

Transmission of drug-resistant HIV and ARV choices

The first case of transmission of drug-resistant HIV was reported in December 1994. In a female previously on ZDV monotherapy until pregnancy, ZDV was re-introduced a few weeks prior to delivery in an attempt to interrupt vertical transmission. The infant was HIV infected with the same mutation documented in the mother prior to pregnancy [81]. The first case of transmission of multidrug-resistant HIV was documented in 2001. Both the infant and the mother had multiple mutations for nucleoside reverse transcriptase and protease inhibitor mutations [82]. Nevirapine (a NNRTI) resistant mutations can be transmitted *via* breast milk [83]. Acquired NVP resistance is the norm in HIV-infected infants who have received extended NVP prophylaxis. These children are often also resistant to second-generation NNRTIs. Transmitted resistance was described in three (12%) out of 25 infants in Panama. NRTI and NNRTI mutations were most common [84].

There are limited data on ARV choices in infancy and less so in the presence of suspected or confirmed ARV resistance. Updated ARV information should be obtained to guide choices [63]. Protease inhibitors such as lopinavir/ritonavir have a high threshold for developing resistance but should only be given from 42 weeks post-conception, whereas NNRTIs have a very low barrier for developing resistance [63].

The most important component of ART success is adherence. A recent review and meta-analysis of adherence to ART during and after pregnancy in low-, middle- and high-income countries involving 20 153 females revealed that only 74% of pregnant females achieved >80% ART adherence. In the postpartum period, this had declined to 53% [40]. Reasons for poor adherence are multifactorial and have physical, economic and emotional causes.

The HIV-exposed uninfected infant

HIV-exposed uninfected infants born to HIV-infected females are also at greater risk of morbidity and mortality than HIV-unexposed infants [85]. The reasons for this are multifactorial and include illness in the mother, exposure to pathogens such as *M. tuberculosis* [86] and also exposure to ART *in utero* [38]. HIV exposure itself may also be immunosuppressive [87, 88]. PCP [89, 90] and other serious infections, such as CMV colitis and congenital CMV infection, have been documented [91]. Breast-fed infants remain at risk of vertical transmission of HIV and require close monitoring. Formula feeding increases the risk of gastroenteritis and pneumonia [18]. HIV-exposed uninfected infants remain at risk of vertical transmission during breastfeeding and require regular testing until 6 weeks after weaning. Long-term follow-up of HIV-exposed uninfected infants is advisable.

Table 2. Optimal approach in pregnancy, delivery and breastfeeding

Factors	Procedures	Comments
Maternal	Early diagnosis ART initiation from 20 weeks' gestation	Check adherence Best confirmation is declining and then undetectable viral load Consider resistance testing for unsuppressed viral load
	Regular retesting of HIV-negative females in pregnancy, labour and during breastfeeding	Rapid antibody tests may be negative in the first 8 weeks after acute HIV infection
Infant at very low risk[#]	Follow national guidelines for infant diagnosis and prophylaxis	PCR should be repeated at least 6 weeks after discontinuing prophylaxis Zidovudine or nevirapine for 6 weeks
Infants at high risk[¶]	Diagnostic PCR on day 1	If very early PCR is negative, repeat PCR after completing post-exposure prophylaxis and then between 2 weeks and 2 months later
	Commence triple antiretroviral prophylaxis as soon as possible after birth	Test for viral resistance in infants failing antiretroviral prophylaxis

[#]: mother on suppressive ART throughout pregnancy or from 20 weeks' gestation; [¶]: maternal viral load not suppressed at delivery acute maternal HIV.

Conclusion

The successes in prevention of mother-to-child transmission allow for more attention to be given to identifying and treating the HIV-exposed and infected infant. For this, early identification of the mother's HIV status during pregnancy is essential, together with prompt initiation of ART. For the newly diagnosed and those already on ART, adherence with regular viral load monitoring is essential. For females testing HIV-negative in pregnancy, repeated testing is essential. Point-of-care viral load tests may, in the future, identify acute HIV infection during pregnancy, labour and post-delivery during breastfeeding (table 2).

Prompt initiation of post-exposure prophylaxis, consisting of three ARVS, is essential for the HIV-exposed infant born to a mother at increased risk of transmitting HIV. Although options are limited, careful consideration should be given to the choice of ARV for neonatal post-exposure prophylaxis when mothers are failing their ART. Diagnostic PCR should be undertaken in the newborn infant as soon as possible after birth and should be repeated at least twice over a period of 2 weeks to 2 months after post-exposure prophylaxis has ended.

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A paediatric perspective

Robin J. Green, Adèle Pentz, Jessica Kolberg and Refiloe Masekela

Pulmonary infectious diseases are common in HIV-infected children and a number of studies have documented both prevalence and aetiology. However, most of these studies highlight a specific disease state. There is no review of the various infectious diseases of the lung that an HIV-infected child may be exposed to over the course of childhood. This review highlights the vast spectrum of pulmonary infectious diseases that impaired immunity makes more probable.

Although bacterial pneumonia is an important disease entity in HIV-infected children, of equal importance is the contribution viruses and fungi make to lung disease in these children. Severe acute pneumonia in HIV-infected infants is known as PCP. This condition requires paediatric intensive care unit admission for ventilation.

Admission to hospital is a frequent event for HIV-infected children with pneumonia. The case fatality rate for this condition is high, in both the general ward and paediatric intensive care. Bronchiectasis is the final end to years of recurrent LRTI in HIV-infected children.

The incidence of HIV infection has increased since the first identified case of HIV in the USA in 1982 [1]. Children acquire HIV *via* three possible routes, namely, *in utero*, *intra partum* (during delivery) and *post partum* (*via* breastfeeding). Perinatal transmission accounts for more than 90% of all childhood infections [2]. The natural history of untreated HIV infection can be rapid progression with death by the age of 1 year, accounting for 25–30% of cases, a milder course with death by the age of 5 years, accounting for 50–60% of cases, or long-term survival beyond the age of 8 years, accounting for 5–25% of cases [2, 3]. These long-term survivors of untreated HIV infection have been referred to as the “slow-progressor” phenotype.

The use of ART together with other interventions, such as an elective caesarean section, avoidance of (or exclusive) breastfeeding and the treatment of concurrent sexually transmitted diseases, can result in a reduction in transmission of HIV to as low as to 1–2% [4–7].

Within the developing world, HIV infection is a significant cause of morbidity in females and their infants. In South Africa 26% of pregnant females are infected with HIV, and in the absence of preventative therapy there is a 15–30% risk of their infants being infected with HIV [6, 7]. Even children who are part of the Prevention of Maternal to Child Transmission

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(PMTCT) programme have an increased risk of HIV infection relative to those who are not exposed, although that risk is substantially reduced.

Mortality in HIV-infected children results primarily from respiratory tract infections [8, 9].

Pulmonary diseases in HIV-infected children

A set of well characterised pulmonary diseases and syndromes occur in HIV-infected children. The age of these children is an important epidemiological predictor of which organism (or set of organisms) is likely to be causing the clinical syndrome of pulmonary disease. Whilst certain infectious diseases are common to all ages (e.g. TB), the vast majority respect age boundaries, consequently age can be very useful when diagnosing the causative organism and hence the nature of the pulmonary condition in this subset of children.

HIV is listed in the South African statistical data as one of the ten leading causes of death, with respiratory tract infections being the third most common cause of death in all age groups [10]. It was estimated that in 2010 there were 120 million episodes of pneumonia in children worldwide and it was suggested that in 2011 some 1.3 million episodes of pneumonia resulted in death [11]. The prevalence of this condition is estimated to be 2–10 times greater in Africa and Asia when compared to the USA [12]. HIV and AIDS have had a significant impact on both the prevalence and severity of CAP, posing a threat to all the gains made on impacting childhood mortality in recent decades [13–15]. CAP in children accounts for between 30–40% of all admissions and has a case fatality rate of 13–20% in HIV-infected children [16, 17]. The natural consequence of the HIV epidemic and the increase in childhood pneumonia prevalence and severity is, therefore, an escalation in the number of hospitalisations for LRTIs and a rise in disease-related morbidity and cost. Costs are not only dictated by the increased number of admissions, but also by the compounded utilisation of diagnostic and therapeutic services for more severe disease.

HIV has, furthermore, impacted on the organisms that cause CAP in children. Besides the common organisms implicated in CAP in HIV-uninfected children, i.e. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Staphylococcus aureus*, Gram-negative pathogens including *Escherichia coli*, *Salmonella* spp., and *Pseudomonas aeruginosa* are pathogenic in HIV-infected children [18, 19]. There is also evidence of higher rates of antibiotic resistance by pathogenic organisms in HIV-infected children [18, 19]. This further contributes to greater morbidity and mortality in this population.

Viral respiratory tract infections are a common occurrence in HIV-infected individuals. Immunological responses to viral infections depend on intact antibody responses, which are impaired in HIV-infected individuals. This is even more pronounced in younger children who may have had no prior exposure to these viruses [20]. The common viruses causing LRTIs i.e. RSV, influenza, rhinovirus, adenovirus and human metapneumovirus, are common in HIV-infected children. However, there is evidence of prolonged shedding of viruses in HIV-infected children with shedding up to 120 days for RSV and 9 months with parainfluenza virus (PIV) infection [21–23].

PCP is a common LRTI in HIV-infected children. The presence of PCP is commonly associated with CMV co-infection [24, 25]. Access to critical care facilities and ART enables HIV-infected children to survive with severe acute respiratory distress syndrome.

WOLFF and O'DONNELL [26] demonstrated a more than two-fold risk of developing bacterial pneumonia in subjects previously treated for PCP.

South Africa has one of the highest burdens of TB in the world, with rates exceeding 5 per 1000 population [7]. Co-infection of TB and HIV has been well described, with HIV being a driver of increased TB prevalence [8, 27]. Unfortunately, the actual co-infection rates are unknown in the paediatric HIV population, due to the lack of acceptable diagnostic tools. The radiological picture and tuberculin skin test have a low diagnostic yield in children, with the majority of children being unable to expectorate sputum [8, 28, 29]. TB can mimic acute pneumonia in all children, especially HIV-infected children, complicating the ability to distinguish it from other causes of CAP [30]. With such challenges in TB diagnostics for HIV-infected children, attempts at TB prevention strategies have yielded disappointing results with current misgivings about the safety of the BCG vaccine in this population [29, 31]. There is contradictory evidence in the literature on the role of isoniazid chemoprophylaxis (IPT). A trial by ZAR *et al.* [32] demonstrated the benefit of IPT, with a statistically significant reduction in mortality in their study population. Conversely, a multicentre trial by MADHI *et al.* [33] showed no benefit of IPT in over 500 HIV-infected infants who were aged less than 1 year. These challenges in diagnosis and prevention of TB result in an under-recognition and paradoxically often over-diagnosis of TB in children infected with HIV.

The utilisation of ART has impacted on the respiratory infectious burden in HIV-infected children, particularly on the pulmonary opportunistic infections [34]. HIV-infected, but untreated, children have an incidence rate of 11.1 per 100 child-years of acquiring acute LRTIs, with ART this decreases to 2.2 per 100 child-years [35]. Therefore, a significant pulmonary morbidity, associated with LRTIs in HIV infection, still persists when compared to HIV-uninfected children. This increased burden, coupled with malnutrition, exposure to pollutants and limited access to healthcare, may result in catastrophic airway destruction and the subsequent development of bronchiectasis in children.

PCP

In HIV-infected and HIV-exposed infants, who present to hospital with acute severe lower respiratory tract disease, a condition known as PCP is usually responsible for the clinical and pathological sequelae. These infants, usually aged between 2 and 4 months, are always hypoxic and require endotracheal intubation and ventilation. A number of pathogens (including *Pneumocystis jirovecii* and CMV) have been isolated. Although there has been considerable focus on *P. jirovecii* as a cause of mortality, the term PCP was retained when *Pneumocystis carinii* was taxonomically renamed *P. jirovecii* [36]), CMV infection has been reported to affect nearly 90% of HIV-exposed infants and especially HIV-exposed infants with severe pneumonia [37].

Admitting HIV-infected infants with severe pneumonia to an intensive care unit (ICU), in a resource limited setting, has created a number of ethical dilemmas for paediatricians. These quandaries are perpetuated by the historical poor outcomes for these patients and the pressure on scarce resources [38]. However, previous reports suggest that this condition can be successfully treated when the mode of ventilation and antibiotic therapy is appropriate for all pathogens that may be present [39].

In South Africa a number of intervention studies have documented how this condition should be managed and, as a result of a clear therapeutic strategy, a case fatality rate of 18% has been achieved; through a meticulous approach to management of the interaction between the host and infection in infants with respiratory failure [40]. In 2004, COOPER *et al.* [41] documented that HIV-infected children admitted to a paediatric ICU in London had 38% mortality after every effort was made to treat such children. All of the patients in a study in Pretoria (South Africa), who were HIV infected, received ventilator assistance and ART early in the course of their disease and survival to 1 year of age appears to be better than reported in previous studies [42].

It appears that at least two major infectious diseases coexist in more severely ill patients with this form of pneumonia, namely *P. jirovecii* and CMV. The interaction of these two organisms in HIV-infected individuals has been suggested in previous reports and in fact CMV appears to be associated with an increased risk of death in most studies [43–47].

Finally, it must be mentioned that therapy for infectious diseases needs to be provided in combination with lung protective ventilation strategies, as for acute respiratory distress syndrome. These strategies include limitation of tidal volume, limitation of peak inspiratory pressure, high peak expiratory pressure, positive end-expiratory pressure, fluid replacement therapy restriction, and early use of steroid therapy.

Until such time as identification, prevention and prophylaxis of HIV in pregnancy is secure in the developing world, it seems prudent to develop a national or international guideline and policy on management of PCP. Current pneumonia guidelines do not routinely include this disease entity.

Bronchiolitis

Bronchiolitis is a disease where infection results in inflammation of the small airways and it occurs most commonly in children under 2 years of age [48]. Most authors and experts agree that the condition has a viral aetiology [49]. The most common aetiological agent is RSV, but PIV (especially type 3), influenza virus, adenovirus and some newer viruses have been identified [50]. Despite the viral nature of this condition, and overwhelming evidence that bacterial co-infections are an extremely rare event [51, 52], most general practitioners and even paediatricians treat infants with bronchiolitis, incorrectly, with an antibiotic.

Bronchiolitis, due to RSV is a disease of young infants in developed countries [53], but there is a suggestion of a later age of involvement in the developing world. The seasonality of bronchiolitis, although conventionally described as a winter disease, is not universal [49].

The clinical diagnosis of viral pneumonia is made more frequently than that of bronchiolitis in HIV-infected children [54]. An altered host-immune response after RSV infection may explain the difference in clinical presentation observed between HIV-infected and uninfected children, with HIV-infected children having more severe disease and more frequent bronchopneumonic changes. Other differences observed in this group of patients include: the risk for developing RSV-associated severe LRTI, which persists beyond the first 6 months of life; and the incidence of concurrent bacteraemia is more common in HIV-infected children [54].

There is now clear evidence that bronchiolitis is not a common condition in HIV-infected infants. In addition, the mean age of bronchiolitis in HIV-infected children is higher than

that of uninfected children in keeping with the findings of earlier studies [55]. The under-representation of HIV-infected children with viral bronchiolitis may have many explanations. Two of these may be that isolated viral bronchiolitis is uncommon in HIV-infected children and secondly that HIV infection confers a greater likelihood of more severe lung disease and bronchopneumonia.

Acute pneumonia

Pneumonia in the developing world remains a major public health concern with a number of children admitted each month to hospital for the management of severe pneumonia. The cost of admission for a patient with CAP is seldom considered in the greater scheme of management strategies and it is an important variable, especially when the cost-efficacy of preventative strategies, such as vaccines, is evaluated.

One prevention strategy, which has shown to be highly successful in the USA, is routine childhood vaccination with PCV. South African studies have shown benefit of this vaccine with a reduction of invasive pneumococcal disease by between 65% and 85% in HIV-infected and HIV-noninfected children, respectively [56].

In addition to the usual risk factors for very severe pneumonia described in the Western World [57], it is important to include HIV infection for children from developing countries [58]. The mortality from pneumonia increases in HIV-infected children with severe CAP and both HIV-uninfected and -infected children with very severe pneumonia (paediatric ICU) [59, 60].

Healthcare systems spend a significant amount of money on procuring antiretroviral treatment for HIV-infected patients and treating the consequences of uncontained HIV disease. These costs are set to escalate unless authorities and medical personnel alike re-enforce preventative strategies, such as reducing mother-to-child transmission of HIV and vaccines that prevent infectious diseases. This should be coupled with reducing new infections in the parents of these children. Only when all preventative strategies are utilised in conjunction will the burden of pneumonia and its attendant will costs decrease. There is mounting evidence that childhood pneumonia is a costly illness [59] and that all efforts should be focused on preventing its occurrence.

Management of acute pneumonia in HIV-infected children is made difficult by the polymicrobial nature of the infection. In a study conducted in Durban (South Africa) the standard use of penicillin and an aminoglycoside for severe pneumonia was more likely to fail in treating the child if the child was HIV infected, and this was noted to be related to the polymicrobial nature of the infection [18]. These authors suggested more broad spectrum antibiotic use and rapid diagnostic testing to define aetiology. There have been repeated pleas for modification of antibiotic policies in HIV-infected children presenting with acute pneumonia [19].

Tuberculosis

TB is a significant organism in the context of HIV infection. Every HIV-infected child with a respiratory tract infection deserves to have TB excluded. In addition to chronic cough and weight loss, South African studies have revealed that TB may present as an acute pneumonia [15]. Diagnosis of TB requires immunological testing, examination of sputa for acid-fast bacilli, culture, and serological testing. In addition to the significant burden of TB disease,

HIV-infected children are at greater risk of acquiring multidrug-resistant organisms [61]. Such organisms make successful therapy significantly more unlikely.

Paediatric TB and HIV have overlapping clinical manifestations, which could lead to missed or late diagnosis. Making a microbiologically-confirmed diagnosis of TB is difficult in children because of the paucibacillary nature of this disease. Rapid PCR tests, such as the Xpert MTB/RIF assay, are increasingly used in children and have been shown to be very effective [62]. Naso-pharyngeal aspirates and stool samples for a PCR-based diagnostic test and mycobacterial cultures are a potential solution to obtaining specimens although yields are significantly less. A four-drug anti-TB treatment should be started immediately at diagnosis, irrespective of the disease severity. Antiretroviral treatment in children should be delayed for 2–8 weeks after initiating anti-TB therapy [63].

In addition to multidrug-resistant TB, the clinical manifestations of TB may be different in HIV-infected children, including a higher percentage of miliary TB and cavitary TB [64]. Problems also exist with TB IRIS and BCG IRIS in HIV-infected children [65]. The management of these conditions is complex and requires appropriate antimycobacterial therapy and systemic corticosteroids are seldom required [66].

TB has been identified in a number of HIV-infected children and adolescents with chronic lung disease, especially bronchiectasis and its role in causation is not clearly elucidated. The presence of TB may reflect a new infection on damaged lungs [67].

Smoking and lung disease

Cigarette smoking has been associated with increased morbidity and mortality in HIV-infected adults [68, 69]. In the Strategies for Management of Antiretroviral Therapy Clinical Trial, 40% of HIV-infected subjects were current smokers [68]. The mortality of these individuals was higher (hazard ratio (HR) 2.4; $p < 0.001$) and there were more serious illnesses and bacterial pneumonia (HR 2.3; $p < 0.001$), in smokers [68].

It appears that the prevalence of smoking is higher in HIV-infected individuals. This has been clearly shown for African HIV-infected individuals [70, 71].

Increased morbidity in smoking HIV-infected adults may take many forms. Importantly smoking increases the risk for secondary infection, including TB [72]. Current smokers were more likely than never-smokers to develop bacterial pneumonia (HR 1.57, 95% CI 1.14–2.15; $p = 0.006$) and oral candidiasis (HR 1.37, 95% CI 1.16–1.62; $p = 0.0002$) [73].

These increased risks have led authors to call for advice on smoking cessation to be incorporated into HIV education programmes and consultations [74].

The natural progression of HIV in children differs from that of adults. Immaturity of the immune system leads to more rapid progression of HIV-related infection [75]. There are various factors that contribute to the rate of HIV progression in children. These include maternal viral load, genetic composition, immunological profile of the child and possibly some environmental factors [76].

Despite expansive literature on the health effects of cigarette smoking in HIV-infected adults, there is only one study, with a limited sample size, which demonstrates an effect of passive

cigarette-smoke exposure on the health of HIV-infected children [77]. This study revealed that rates of cigarette smoking are higher in parents of HIV-infected children than the South African national average [78].

A small study of 127 HIV-infected children attending an HIV treatment clinic in Pretoria, (South Africa) did not reveal statistically significant differences in objective measures for HIV status (CD4 count and HIV stage) between children exposed to environmental tobacco smoke (ETS) and those not exposed [77]. This is in contradistinction to most adult studies and may of course reflect the small sample size.

However, there is no apparent effect of ETS exposure on clinical disease severity as indicated by need for hospitalisation. ETS exposure has been linked to greater risk of asthma exacerbations in asthmatic children [79] and it seems unlikely that this is not true of disease exacerbations in HIV-infected children. It is likely that the health risks of, and diseases associated with, HIV infection are of such a nature to render the additional effects of ETS insignificant.

Bronchiectasis

The exact pathophysiological mechanisms involved in the initiation of bronchiectasis are unknown. The current accepted theory is the “vicious cycle” theory, proposed by COLE [80] in the middle of the 1980s. Cole’s theory evolves around an initial “hit” or “trigger” that results in airway inflammation (fig. 1). The inflammatory process is established such that, with subsequent lung infections, persistent airway inflammation occurs. This is associated with the release of the pro-inflammatory cytokines IL-6, IL-8 and neutrophil elastase [81–83]. These cytokines recruit inflammatory mediators, whose end-product is mucous gland hypertrophy and mucus hyper-production. Excess mucus compromises the mucociliary escalator, which further perpetuates microbial invasion of the airway. Mucus performs an innate immune function in the lungs by acting as the first barrier in the airways. Mucus is made up of mucin proteins, water, surfactant phospholipids, peptides and defence proteins. There are many changes that occur to the mucus properties of patients with chronic inflammatory lung disease [84]. Goblet cell hyperplasia contributes to excessive mucus production. In the presence of infection, epithelial cells modulate the recruitment of inflammatory cells by the production of chemokines, cytokines, adhesion molecules and the modulation of expression of receptors. The presence of persistent infection and impairment of the protective mucociliary escalator as well as the presence of enzymes, such as elastase, results in damaging the airway and lung tissue [85].

It is well known that children infected with HIV are at an 11-fold risk of having acute LRTI and even when treated with ART, these children are still at a two-fold risk of LRTIs, when compared to their uninfected counterparts [86, 87]. Therefore, chronic lung disease, especially bronchiectasis, is often a sequela in these children. However, there may be important other causes or contributors to bronchiectasis and chronic lung disease in these children, including late initiation of ART, immotile cilia, biomass fuel exposure, passive ETS exposure, aspiration, malnutrition, and even the HIV itself [67]. Data from the USA has shown that over 75% of children aged 13 years or older with AIDS receiving ART will survive for at least 9 years [88]. ART availability will, therefore, reduce the number of cases of HIV-related bronchiectasis but the disease may not disappear completely as LRTIs will not cease completely and increased life span makes the number of infections more likely.

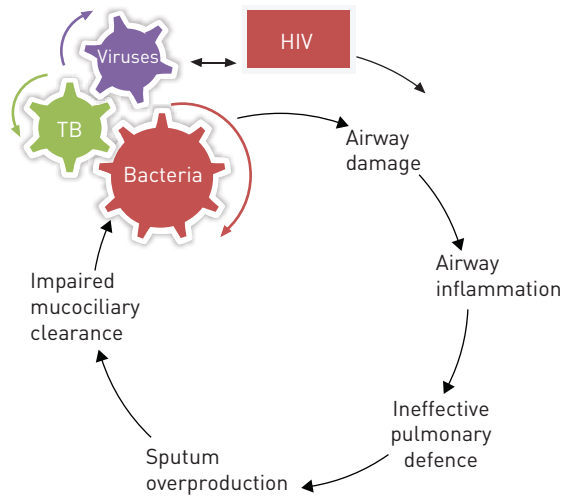


Figure 1. Proposed pathophysiology of bronchiectasis during HIV infection.

Some important clinical findings were reported in a cohort of children with HIV-related bronchiectasis [89]. Children were diagnosed after 6 years of age in this group. It is presumed that the majority of these children had vertical transmission of HIV. This may, therefore, demonstrate a failure of the PMTC programme in these individuals; HIV-infected females and their newborn children were clearly not offered HIV testing, as well as poor post-natal follow-up of HIV-exposed infants. The delayed presentation may have many explanations; including the possibility of the “slow-progressor” phenotype, failed health services or missed diagnosis due to mislabelling as TB.

The anthropometric measurements of children with HIV-related bronchiectasis in this study [89] were within normal limits, the majority of children having acceptable weight, height and body mass index (BMI) z-scores. This occurred despite them having chronic inflammatory lung disease and HIV infection, both of which can increase metabolic demands. The use of ART has been previously shown to positively impact growth parameters in children, with a sustained increase up to 96 weeks after the initiation of treatment [90, 91]. The impact of nutrition on lung morbidity is well described in cystic fibrosis (CF), where the lower the BMI, the higher the morbidity is from lung disease [92].

H. influenzae and PIV are the predominant organisms cultured in children with HIV-related bronchiectasis. In South Africa, *H. influenzae* type B (Hib) vaccination has been universally available for all children since July 1999, with absolute cases of Hib decreasing by 65% in children aged less than 1 year, from 1999–2004; whilst rates of nontypeable *H. influenzae* have increased, especially in HIV-infected children under the age of 5 years [93]. Although, in the context of HIV infection, the Hib vaccine seems to be less effective than in uninfected children, MADHI *et al.* [94] found the Hib vaccine is effective in reducing overall invasive Hib disease by 83% in all children.

S. aureus was also not a major pathogen in this study population. McNALLY *et al.* [95] found that the risk of *S. aureus* nasal carriage (and, therefore, predicted sepsis) was 2.86 times higher in HIV-infected children presenting with CAP [95]. A systematic review of causes of CAP also revealed a 2.5-fold risk of *S. aureus* infection [96]. Although, this pathogen seems to

have a major role in CAP for HIV-infected children, it does not seem to be a major pathogenic organism in HIV-related bronchiectasis.

More than three quarters of the study population had a prior diagnosis of and treatment for TB. The challenges of accurate TB diagnosis in HIV-infected children are well documented, and in a high TB burden area there may be an over-reliance on radiological diagnosis [86, 97]. The limitation of this approach is the result of TB having a similar radiological picture to bronchiectasis and, therefore, may explain how bronchiectasis could have been missed in some children. Coupled with this, children with bronchiectasis may also present with *Mycobacterium* other than TB infections, which may be mislabelled as *Mycobacterium tuberculosis* [98]. In the study by MASEKELA *et al.* [89] almost a quarter of children had received two courses of anti-TB treatment. This is not surprising, as the current guidelines for TB diagnosis at the primary healthcare level depends heavily on chest radiograph interpretations and the presence of a chronic cough for more than 2 weeks [99]. The study by MASEKELA *et al.* [89] suggests that an important differential diagnosis to TB in HIV-infected children, with recurrent chest symptoms, is bronchiectasis. Consequently there is an urgent need for a guideline to be devised to help identify children with bronchiectasis.

Respiratory morbidity from HIV-related bronchiectasis is significant, with accelerated pulmonary function decline. It is suggested in the study by MASEKELA *et al.* [89] that the median FEV₁ was 53% pred; this is in comparison to a population of New Zealand children with non-CF bronchiectasis, where the authors reported a baseline FEV₁ of 66% pred [100]. HAIDOPOULOU *et al.* [101] also reported an FEV₁ of 75% pred in a group of children with bronchiectasis secondary to primary immunodeficiency, although their study population had been diagnosed with primary immunodeficiency at a median age of 3.5 years. A possible explanation for the lower pulmonary function measurement, observed in the study by MASEKELA *et al.* [89], is that even in the presence of ART there is still a significantly higher risk of exacerbations that are related to the abnormal immune response to pathogens in HIV-infected individuals [102].

A significant proportion of the children in the MASEKELA *et al.* [89] study were exposed to biomass fuels (BMF). Exposure to BMF is known to impact on lung health. Not only does it increase the risk of acute LRTIs but it also has a local effect on the bronchial epithelial layer, by increasing bronchial inflammation and reducing mucociliary clearance, which in turn, increases the residence time of inhaled particles [103–105]. This may be an additional factor accounting for the lower pulmonary functions in this cohort [89], and may, therefore, be a potential risk factor for children developing recurrent chest infections.

The management of non-CF bronchiectasis has not been fully elucidated. It appears that the principles employed in CF must be followed. These include: daily physiotherapy; regular clinic visits; regular culture of respiratory secretions, in order to determine the likely pathogens; and, finally, early treatment of exacerbations. What is important to recognise is that in this form of HIV-related bronchiectasis, the pathogens are different to those of CF and treatment to cover *H. influenzae* and *H. parainfluenzae* need to be considered. Since β -lactamase production occurs in these organisms the addition of clavulanic acid to amoxicillin should be considered.

Lymphocytic interstitial pneumonia

LIP is potentially an infectious disease since it has been linked to EBV infection, which results in a chronic lymphocytic infiltration of the lungs. Cough is the main symptom and severe

respiratory signs are usually absent [106]. Lymphoproliferation results in generalised lymphadenopathy, bilateral non-tender parotid enlargement, and enlargement of the liver or spleen [86, 107, 108]. Clubbing of the fingers and toes is common. Chest radiographs often show a diffuse reticulonodular pattern [109]. Treatment should include the initiation of ART and oral corticosteroids should only be indicated if children are severely symptomatic or hypoxic [110].

Additional infections and conditions

Recent literature has focused attention on a new range of infectious and noninfectious consequences in HIV-infected children. Reports have emerged of cryptococcal antigenemia, at least in HIV-infected adults, even in the absence of meningitis and patients presenting only with pneumonia [111]. Non-mycobacterial TB is significantly more likely to be identified in HIV-infected children and may cause pneumonia [112]. This disease carries a poor prognosis. A Zimbabwean study identified bronchiolitis obliterans as the most common cause of chronic lung disease in HIV-infected adolescents. These authors speculate that the condition is caused by multiple bacterial and/or viral infections or even the HIV infection itself [113]. Another group working in Zimbabwe found that cardiac dysfunction was common in HIV-infected adolescents, with left ventricular dysfunction in one-third and right ventricular dysfunction in 29% of this group of adolescents [114].

Conclusion

The HIV-infected child is at risk of a life-time of respiratory tract infections. These range from early PCP, through bacterial CAP and viral bronchiolitis, to TB and ultimately damaged airways with colonisation of bronchiectic lungs. Ideally a programme of successful PMTC must halt this disease but even early introduction of ART will retard the relentless progression of lung disease.

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Bacterial community-acquired pneumonia

Charles Feldman¹ and Ronald Anderson²

Bacterial CAP remains an important cause of morbidity and mortality in HIV-infected patients. Smoking is a major risk factor and daily smoking attenuates the immunological and virological responses to ART by 40%. The bacterial pathogens causing CAP in HIV-infected patients are largely similar to those in HIV-uninfected patients. The clinical presentation in HIV-infected patients is also similar to that of HIV-uninfected patients, although in severely ill HIV-infected patients with bacteraemic pneumococcal CAP, the mortality appears to be higher than in HIV-uninfected patients, with a trend towards increasing mortality in those with lower CD4 cell counts. Empiric antibiotic treatment commonly recommended in HIV-infected patients with bacterial CAP is either a β -lactam/macrolide combination or fluoroquinolone monotherapy. Following recovery from an episode of bacterial CAP, HIV-infected patients may have a worse progression of their HIV disease and permanent declines in lung function. Careful consideration needs to be given to the prevention of CAP in HIV-infected patients, including smoking-cessation strategies and vaccination.

The lungs are the most common site of infection resulting from HIV. Pulmonary infections remain one of the most important causes of both morbidity and mortality in these individuals [1, 2]. It is also recognised that the epidemiology of HIV-related pulmonary infections has changed as a consequence of advances in the management of patients infected with HIV; however, the common respiratory infections are TB, PCP and CAP [1, 3, 4]. PCP has decreased considerably since the early days of HIV infection, with the use of co-trimoxazole prophylaxis and the introduction of ART. TB has also decreased in developed countries, such that bacterial pneumonia is the most common respiratory infection in these regions. However, in many parts of the developing world, including sub-Saharan Africa, TB remains the most common respiratory infection in HIV-infected patients, with CAP second [1, 2, 5, 6]. An important aspect of bacterial CAP is that it may accelerate the course of HIV disease and it is said to be an independent risk for progressive immunosuppression and mortality in HIV-infected patient [3].

The objective of this chapter is to review the topic of bacterial CAP in HIV-infected patients, describing the risk factors, common bacterial pathogens, clinical presentation, diagnosis, treatment, outcome and prevention of these infections.

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Bacterial CAP

Bacterial pneumonia has been clearly recognised as a major cause of LRTI in HIV-infected individuals, irrespective of their degree of immunosuppression, although there is an inverse relationship between CD4 cell count and pneumonia risk, the greatest risk is at a CD4 cell count less than $200 \text{ cells} \cdot \mu\text{L}^{-1}$ [7, 8]. This increased risk is not only due to the HIV infection itself, but occurs particularly in association with intravenous drug use, smoking and alcohol abuse. It remains true in many studies, even those conducted after the introduction of ART, although some studies have suggested that the persistently increased incidence of pneumonia is only in those specific high-risk patients [7, 9–12]. For example, one study of 885 HIV-infected females documented a rate of bacterial pneumonia of 8.5 cases per 100 person-years compared with 0.7 cases per 100 person-years in HIV-uninfected females, and while co-trimoxazole prophylaxis and ART decreased this risk, smoking doubled the risk, such that high rates of bacterial pneumonia persisted and were associated with accelerated progression to death [13].

HIV-associated immune dysfunction

The upper and lower airways are extremely well equipped with varied host defences, both innate and adaptive, which confer efficient protection against respiratory pathogens. During HIV infection, these undergo progressive attrition, albeit at a slower rate than that of the gastro-intestinal tract, primarily as a consequence of depletion of CD4^+ T-helper (Th) lymphocytes. The resultant immune dysfunction is characterised not only by seriously impaired efficacy of T-cell dependent production of specific antibodies, but also of cell-mediated immune responses orchestrated by Th1 and Th17 cells, which promote monocyte/macrophage and neutrophil recruitment and activation [2, 14, 15]. The consequence is a marked increase in susceptibility to the development of bacterial pneumonia, which, in the case of pneumococcal pneumonia in particular, is exacerbated by cigarette smoking and recent influenza virus infection, both of which intensify pulmonary immune dysfunction [16–19]. Failure of antibody-mediated neutralisation of the antiphagocytic polysaccharide capsule of the pneumococcus, as well as ineffective antibody- and cell-mediated immune responses to pneumococcal protein virulence factors, underpin the susceptibility of those infected with HIV to this dangerous bacterial pathogen.

Risk factors for CAP

A myriad of studies has documented the risk factors for CAP in HIV-infected persons and these are indicated in [table 1](#) [1, 2, 7–9, 20–28].

In one study, a CD8 T-cell level less than $400 \text{ cells} \cdot \mu\text{L}^{-1}$ was also associated with an increased risk of pneumonia and of all-cause mortality in HIV-infected females [29]. Also, in patients on cART, higher levels of systemic inflammatory markers have been documented to be associated with an increased risk of bacterial pneumonia [30]. Underlying comorbid conditions predisposing to bacterial CAP in HIV-infected persons include cardiovascular diseases, renal diseases, respiratory diseases and hepatic cirrhosis. Daily tobacco use has been shown to attenuate the immune and virological response to ART by 40% and also to predispose not only to CAP, but also to PCP and TB [23]. Smoking cessation appears to be associated with a significantly decreased risk of bacterial pneumonia [17, 31].

Table 1. Risk factors for CAP in HIV-infected patients

• Genetic factors • Race • Low socioeconomic status • Malnutrition • Increased age • HIV infection <i>per se</i> • Degree of immunosuppression, CD4 cell count • Detectable viral load	• Intravenous drug use • Tobacco use • Underlying comorbid illnesses • Neutropenia • Splenectomy • Previous pneumonia • Low Karnovsky score • Not receiving ART
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Aetiology of CAP in HIV-infected patients

Bacterial CAP occurs more commonly among HIV-infected individuals and the spectrum of pathogens, in general, does not differ significantly from those patients who are not infected with HIV [32]. A specific aetiological diagnosis is made in approximately 35% of cases, varying in the different studies from 21% to 55% [21].

Streptococcus pneumoniae (pneumococcus)

As in HIV-uninfected individuals, the most common bacterial cause of CAP in those infected with the virus is the pneumococcus, which has been said to account for 20% of bacterial pneumonia cases overall (40% of documented-aetiology cases) [1]. Important features of pneumococcal CAP in HIV-infected persons include a high rate of bacteraemia and of recurrent infection [1]. In one study of HIV-infected patients with CAP, bacteraemia was present in 24% of the cases and independent predictors of bacteraemia included the detection of pneumococcal antigens in the urine, and absence of ART [33]. Clearly it is recognised that HIV infection is among the risk factors for invasive pneumococcal disease (IPD) and should be tested for in cases with pneumococcal bacteraemia even in the absence of any other recognised IPD risk factors [34]. Mortality is said to be higher in these cases with pneumococcal infection and bacteraemia.

With improvements in the overall management of HIV-infected persons, there has been some debate about the incidence of IPD in these cases. Some studies have documented a substantial decrease in incidence with the use of ART and pneumococcal vaccine, although the risk factors for, as well as the outcome of, pneumococcal bacteraemia remain similar to those for HIV-uninfected individuals [20, 35, 36]. However, other studies, including one from South Africa, have documented a high remaining burden of IPD despite a stable prevalence of HIV infection and a progressive roll-out of ART [1, 37]. A number of other studies have also documented high residual rates of IPD despite introduction of ART [38]. It has been suggested that IPD risk in HIV-infected persons is 30–100 times more common than in HIV-uninfected cases [39]. An additional investigation that confirmed a high incidence of IPD in HIV-infected patients, despite the widespread use of ART and of PPV, also documented that this was associated with high morbidity and mortality [40]. It has been suggested that the potential role of the pneumococcal conjugate vaccines, both in children and possibly in HIV-positive adults, needs to be considered as a strategy to reduce IPD among these adults [41].

It is not always easy to differentiate clinically the various microbial causes of community-acquired respiratory infections in HIV-infected cases and a number of studies have attempted to address this issue. One investigation, which was a prospective observational study of 331

consecutive HIV-infected adults with CAP, documented that the pneumococcus was the most common organism in the group of patients with CD4 cell counts greater than 200 cells· μL^{-1} , whereas *Pneumocystis jirovecii* was most common at CD4 cell counts below 200 cells· μL^{-1} [42]. Predictors for bacterial CAP were: symptoms for 5 days or less, a C-reactive protein level of 22 mg·dL⁻¹ or greater and a hepatitis C co-infection [42]. Others have documented that significantly higher procalcitonin and C-reactive protein levels are found in HIV-infected patients with pneumococcal CAP, when compared to those with TB, and may be useful in differentiating these two infections [43].

Important observations in HIV-infected patients with pneumococcal CAP include a significant depression of the CD4 count during the acute phase of the infection (in patients not on ART) with a subsequent increase in levels in most following successful treatment of the pneumococcal infection alone [44], and dual infections with *Mycobacterium tuberculosis* and *S. pneumoniae* in HIV-infected patients with CAP [45]. Other investigators have also documented secondary infections, including those due to the pneumococcus, to be relatively common in patients with HIV infection and with TB, and among those with TB/HIV co-infection [46]. Furthermore, it is recognised that increased pneumococcal bacterial loads, such as determined by measurement of quantitative real-time PCR (using pneumococcal *lytA* detection) are associated with more severe outcomes, and at least one investigation has documented that HIV infection is associated with an elevated pneumococcal load, itself associated with an increased risk of death [47]. Lastly, the controversial issue of pneumococcal vaccination in HIV-positive patients is discussed in more detail later in this chapter [1].

Haemophilus influenzae

Haemophilus influenzae, which is considered to be the second most common cause of CAP in HIV-infected patients, is said to account for up to 10–15% of bacterial CAP of known aetiology [1]. In some studies, HIV infection itself has been the most common underlying risk factor for *H. influenzae* infection [48]. The characteristic features of *H. influenzae* include: an ability to cause infection in those with advanced immunosuppression; an association with a subacute presentation in 30% of cases; an occasional association with a diffuse interstitial pulmonary infiltrate, similar to that of PCP; and an association with a low mortality, similar to that in the general population, with a low propensity for recurrence [1, 49, 50].

Staphylococcus aureus

It is said that this pathogen is the third most common cause of bacterial CAP [1]. Significant independent risk factors for this infection include *i.v.* drug use and previous PCP infection [51]. One study documented that the chest radiograph commonly showed evidence of lobar pneumonia, predominantly in the lower lobes (78%), pleural effusion present in some 30% of cases, and although response to therapy was often good (79% response to therapy), recurrence occurred in a number of cases (26%) and death in some 21% of patients [51]. HIV-infected patients appear to be at increased risk of community-acquired methicillin-resistant *S. aureus* infections, some of which manifest as CAP [52, 53]. A confirmed case of CAP due to Panton-Valentine leukocidin-producing *S. aureus* has also been documented in an HIV-2-infected patient [54].

Gram-negative pathogens

Earlier studies suggested that infections with *Pseudomonas aeruginosa* occur, including both nosocomial and community-acquired infections (the latter mainly in those with advanced

immunosuppression); however, these infections appear to be much less common in the ART era [1, 55–60]. HIV-infected patients with pseudomonal pneumonia tend to have lower leukocyte and CD4 cell counts and are much more likely to become bacteraemic than the general population [57, 60]. Recurrent infections may occur in those with chronically depressed CD4 cell counts, which may resolve after effective ART and with the use of adequate antimicrobial therapy [58, 60]. The changes found on chest radiographs may include interstitial shadowing mimicking PCP [55]. The mortality rate of these infections is higher in patients with advanced HIV disease [56]. Infections with *Klebsiella pneumoniae* have also been described in patients with advanced HIV disease [8].

Legionella infections

Legionnaire's disease occurs more commonly in patients with some degree of immunosuppression, but it has been documented relatively infrequently in patients who are HIV infected, and there is doubt as to whether HIV infection is a particular risk factor [8, 61]. However, some studies have suggested that this infection may occur 40 times more frequently in HIV-infected patients than in the general population [1]. In HIV-infected persons, the infection has often been documented to be more severe, with a more complicated course, and with a higher rate of respiratory failure and increased mortality [61, 62]. One study compared epidemiological, clinical and outcome data of CAP patients with pneumococcal infections versus *Legionella pneumophila* pneumonia [63]. *Legionella* infections were more commonly associated with a higher mean CD4 cell count, an undetectable viral load and the use of ART, and were more severe with extrapulmonary symptoms, bilateral lung radiological involvement, respiratory failure, the need for mechanical ventilation and had a greater risk of death [63]. One Danish study suggested that infections with *L. pneumophila* were rare in their HIV-infected patients, despite using PCR-based assays for diagnosis [64].

Other atypical pathogens

The true prevalence of infections with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in HIV-infected persons is uncertain, although they appear to be relatively uncommon [1, 65]. A Danish study [64] suggested that they appeared to be rare in their HIV-infected cases, while another study suggested that there may be a high incidence of CAP due to *C. pneumoniae* in a cohort of former drug users [66]. An Italian study documented *C. pneumoniae* as a possible cause of severe respiratory failure in HIV-infected patients and the authors of both this and the Danish study suggested considering these pathogens in patients with CAP who are not responding adequately to standard therapy [64, 67].

Moraxella catarrhalis

There have been relatively few cases of CAP due to *M. catarrhalis* infection in the literature but some studies have suggested that when it occurs in HIV-infected patients it may be associated with considerable morbidity, especially in the presence of a low CD4 cell count or coexisting lung disease [68].

Rhodococcus equi

The Gram-positive organism *Rhodococcus equi* is an uncommon cause of CAP in HIV-infected humans, and when it does cause infection it characteristically presents as cavitary

pneumonia in those with a low CD4 cell count [69]. While outcomes of this infection were relatively poor in the pre-ART era, related primarily to relapses rather than mortality, favourable responses have been documented with use of ART and combination antibiotic therapy [69].

Clinical presentation of pneumonia

In most patients, the clinical presentation of CAP in HIV-infected cases is very similar to that in HIV-uninfected cases, with symptoms of fever, cough with sputum production, chest pain and shortness of breath, and clinical signs that are no different; although there are few studies that have comprehensively studied this [8]. Differences that were noted in one study of patients with pneumococcal pneumonia were that HIV-infected cases were younger and had more clinical symptoms, especially among those patients with lower CD4 cell counts (including rigors, pleuritic chest pain, cough, sputum production, haemoptysis, diarrhoea, vomiting and headache) [70]. Other important differences in presentation when comparing HIV-infected and HIV-uninfected cases are: there is a higher rate of bacteraemia in the former infections; unusual radiographic changes are not infrequent, including a high rate of pleural effusions; and a higher rate of opportunistic pathogens are isolated, as described earlier [8]. With regard to radiological differences, it has been mentioned previously that certain of the common pathogens may have an unusual radiographic presentation, including a diffuse infiltrate with *H. influenzae* infections and cavitation in *R. equi* infections [2]. Furthermore, the study on invasive pneumococcal pneumonia described earlier documented a higher rate of bilateral lung involvement among HIV-infected individuals [70]. Certainly, there is no evidence that HIV-infected persons with pneumococcal pneumonia are necessarily more severely ill than HIV-uninfected cases [70] and the various severity of illness scoring systems, including the Pneumonia Severity Index and CURB-65 score (confusion, urea >7 mmol·L⁻¹, respiratory rate ≥ 30 breaths per min, blood pressure, 90 mmHg (systolic) or ≤ 60 mmHg (diastolic), age ≥ 65 years) appear to equally valid in HIV-infected cases [2, 71–73]. It is also important to remember that there is a greater risk of antibiotic resistance among the commonly isolated pathogens, including the pneumococcus, although discussion of the possible impact of this is beyond the scope of the current review [9].

Laboratory diagnosis

In HIV-infected patients presenting with classical clinical features of bacterial pneumonia, many clinicians will initially perform standard radiological, microbiological and other laboratory investigations, and only proceed to more invasive diagnostic techniques for those cases that do not respond well to initial empiric treatment. Notwithstanding traditional microbiological methods, which are of limited value in the detection of fastidious, slow-growing, difficult-to-isolate bacterial pathogens, a number of pathogen surface antigen/nucleic acid-based procedures are available for a more rapid detection of respiratory pathogens in biological samples from patients with either HIV-infected or -uninfected CAP. Well accepted antigen-based assays include: 1) Binax NOW immunochromatographic procedures (Thermo Fisher Scientific, Remel Microbiology Products, Lenexa, KS, USA) for the detection of pneumococcal capsular polysaccharide and *L. pneumophila* antigens in urine, as well as in cerebrospinal fluid (CSF) in the case of the latter [74]; and 2) the Pneumotest-Latex (Randox Molecular Diagnostics, Crumlin, UK) for detection of pneumococcal capsular polysaccharide antigens in blood and CSF [75]. As mentioned earlier, RT-PCR procedures based on the detection of the *lytA* (autolysin) gene of the

pneumococcus in blood and sputum are of importance not only in pathogen detection, but also in the measurement of bacterial load, a significant indicator of disease severity and outcome [76, 77]. A number of multiplex PCR-based procedures are also available for the detection of CAP pathogens. One of these, recently introduced by Randox Molecular Diagnostics, enables the simultaneous detection of seven CAP bacterial pathogens (*C. pneumoniae*, *H. influenzae*, *L. pneumophila*, *M. catarrhalis*, *M. pneumoniae*, *S. aureus*, *S. pneumoniae*) and 15 viral pathogens in bronchoalveolar lavage, sputum and saliva specimens, as well as nasopharyngeal swabs. The performance and reliability of this procedure in the clinical setting remains to be established.

Measurement of nonspecific, host-derived, circulatory biomarkers of infection, such as procalcitonin, may also have some value in guiding diagnosis, response to antimicrobial therapy and predicting outcome, as mentioned earlier [78].

Treatment of CAP

There are currently no specific guidelines addressing the issue of antibiotic treatment of HIV-infected patients with CAP, although some guidelines do have sections addressing the question of the various aspects of management of these cases [21, 79]. In general terms the antibiotic treatment of bacterial CAP in HIV-infected patients will be very similar to that in HIV-uninfected cases and is aimed at covering the most likely pathogens, while being cognisant of their likely antimicrobial susceptibility patterns and being modified according subsequent laboratory results [2, 79]. In general, the use of a β -lactam/macrolide combination regimen or fluoroquinolone monotherapy is commonly recommended [2, 80]. Although some studies have suggested that addition of a macrolide to the β -lactam agent is not associated with a better outcome than β -lactam therapy alone [81], one very large prospective, observational study of patients, with and without HIV infection, who had pneumococcal bacteraemia, predominantly pneumonia, documented that combination antibiotic therapy was associated with a significantly lower 14-day mortality in severely ill cases [82]. This association remained even with the evaluation of the subset of HIV-infected cases alone. Caution needs to be raised with regard to the use of fluoroquinolone monotherapy in areas where TB is common, since its use in cases with suspected CAP, who actually have TB, may potentially be associated with either masking TB diagnosis due to rapid clearance of the TB organisms from the sputum, and/or subsequent development of fluoroquinolone resistance among the TB isolates [2].

Adjuvant therapies

The primary objective of adjuvant therapy in CAP is to control harmful pathogen-activated inflammatory responses, predominantly neutrophil mediated, which are believed to contribute significantly to morbidity and mortality. Currently, macrolides and statins are the most favoured anti-inflammatory therapies for CAP while the role, if any, of corticosteroids remains contentious [83, 84]. Notwithstanding the use of corticosteroids in patients with moderate-to-severe PCP [32], as well as a possible niche role in the treatment of mild-to-moderate paradoxical TB-IRIS [85], corticosteroids are used discerningly in the setting of a HIV infection.

Macrolides possess an unusual dual mechanism of anti-inflammatory activity. First, these agents, which target bacterial protein synthesis, inhibit the production of pro-inflammatory

bacterial virulence factors. Moreover, because they are primarily bacteriostatic, unlike β -lactams, they do not exacerbate harmful inflammatory responses by causing rapid disintegration of bacilli. Secondly, macrolides also possess secondary anti-inflammatory properties, unrelated to their primary antimicrobial activity. These agents directly target the production of the neutrophil-mobilising/-activating chemokine, IL-8, and the cytokine TNF- α , by cells of the innate immune system, as well as structural cells [86]. Pathogen- and host-directed anti-inflammatory activities of macrolides are, therefore, believed to underpin their clinical utility in the treatment of CAP, including HIV-associated CAP [82]. However, widespread acceptance of the benefit of macrolides as an adjunct to β -lactams in the therapy of CAP is dependent on the outcome of large, well-controlled, multicentre, randomised clinical trials. One such study, recently completed, is the Community-Acquired Pneumonia Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START), the results of which are awaited [87].

It is noteworthy that progressive HIV infection results in chronic, systemic activation of neutrophils. This, in turn, is associated with increased generation of ROS and the release of arginase-1 and other granule enzymes, as well as high-level surface expression of the programme death ligand-1 on neutrophils. All of these mechanisms exacerbate immunosuppression [88, 89]. It is, therefore, conceivable but largely untested, with the exception of the study by BADDOUR *et al.* [82], that macrolides may be of particular benefit in the clinical setting of HIV-associated CAP.

Statins are inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase and are used primarily to control hypercholesterolaemia in the prevention of cardiovascular disease and stroke. Like macrolides, these agents also possess secondary anti-inflammatory properties, targeting neutrophils and other types of inflammatory cell *via* inhibitory effects on intracellular signalling mechanisms linked to the activation of genes encoding various inflammatory mediators [83, 90]. A number of clinical studies have reported a decreased risk of development of CAP, as well as decreased mortality from CAP [83, 90, 91], including pneumococcal pneumonia [92], for current statin users. However, once again the acceptance of the role of statins as an adjunctive therapy in CAP is dependent on the performance and outcome of large, randomised, controlled clinical trials [90, 91].

To our knowledge, no studies on the effects of statin use on the frequency and outcome of HIV-associated CAP have been reported. It is noteworthy, however, that statin use by HIV-infected individuals has been reported to be associated with a significant reduction in non-AIDS-defining malignancies [93], as well as reduced mortality in those with a diagnosis of a concomitant comorbidity (cardiovascular, renal and diabetes) [94].

Outcome of CAP in HIV-infected cases

The mortality of HIV-infected patients with bacterial pneumonia is in the order of 10–15%; however, there is still considerable debate as to whether the outcome of all-cause CAP and of pneumococcal CAP is different in HIV-infected and HIV-uninfected cases [2, 8, 21]. A number of studies have suggested that, with regard to all-cause CAP, HIV status has no impact on outcome, with one study additionally suggesting that CD4 cell counts and HIV-RNA levels did not predict the likely outcome [95–97]. However, data are less clear with regard to pneumococcal CAP [2, 70, 98]. Earlier studies seemed to suggest that the outcome of pneumococcal pneumonia was similar in HIV-infected *versus* HIV-uninfected cases [2, 98, 99], while a more recent study documented otherwise [70]. In the latter study of 768 cases

with bacteraemic pneumococcal CAP, although initial analysis indicated that 14-day mortality was no different in HIV-infected and HIV-uninfected cases, when adjustments were made for age and severity of illness, HIV-infected patients had a higher mortality, with a significant trend for increasing mortality in those with lower CD4 cell counts [70]. For this, and other reasons, a number of investigators recommend admission to hospital for all HIV-infected patients with bacterial CAP and a CD4 cell count below 200 cells· μL^{-1} , whereas in those with a CD4 cell count ≥ 200 cells· μL^{-1} , admission decisions should be based on severity of illness assessment (*e.g.* using a severity of illness score) [21].

It is also important to consider that there are other impacts of an episode of bacterial pneumonia in HIV-infected cases even in cases that recover from the acute illness. Studies have clearly shown that bacterial CAP (like PCP infection) is associated with a significantly worse HIV course following recovery from the initial infection, with regard to medium term survival, subsequent occurrences of AIDS-defining opportunistic infections and neoplasia [100]. Furthermore, both bacterial CAP and PCP are associated with significant and permanent reductions in lung function parameters after the acute infection is resolved [101]. All these issues highlight the importance of prevention of these infections using the various measures available.

Immunisation strategies

Of the various CAP bacterial pathogens, immunisation against pneumococcal disease is a definite recommendation for those infected with HIV, irrespective of the circulating CD4⁺ T-cell count, with one possible exception that is mentioned later [102]. The primary objective of pneumococcal vaccination is to elicit the production of capsule-targeted opsonophagocytic antibodies. Pneumococcal vaccines are of two types. First, those containing a cocktail of unconjugated capsular polysaccharides (*i.e.* PPVs), based on prevalence and virulence of the vaccine serotypes. Secondly, those in which the capsular polysaccharides are conjugated to a nontoxic, immunogenic carrier protein (*i.e.* PCVs), usually diphtheria toxoid. PPVs and PCVs elicit T-cell independent and dependent antibody responses, respectively. The current leaders in these two vaccine categories are PPV23 introduced in the middle of the 1980s, and PCV13 introduced in the USA in 2010 and in many other countries thereafter. This latter vaccine has largely replaced its predecessors PCV7 and PCV9.

In an earlier clinical study conducted between October 1995 and June 1998, 1372 Ugandan HIV-infected patients were randomised to receive a single injection of either PPV23 or placebo, with the primary end-point being a first episode of IPD [103]. Administration of PPV23 was found not only to be ineffective, but surprisingly was also associated with a significant increase in all-cause pneumonia, but not mortality [103]. However, in a 6-year follow-up study, the authors reported that vaccine recipients exhibited “a significant survival advantage following vaccination,” in the setting of a persistent excess in all-cause pneumonia [104].

In the case of PCVs, two studies, one undertaken in HIV-infected and uninfected children (PCV9), and the other in HIV-infected adults (PCV7), reported that immunisation conferred significant protection against a first episode of invasive disease in the former study [105], and against recurrent infection by vaccine serotypes, as well as protection against a non-vaccine serotype (6A) in the latter [106].

Although the efficacy of PCV13 in the setting of HIV infection remains to be established, the US Advisory Committee on Immunization Practices issued recommendations in 2012 with

respect to administration of PCV13 to individuals aged 19 years or older with immunocompromising conditions. These are based on a “prime–boost” strategy involving primary immunisation with a single dose of PCV13 followed at least 8 weeks later by a single dose of PPV23 [102]. Although this recommendation is applicable to all vaccine-naïve, HIV-infected patients, it has also been proposed that the administration of PPV23 be deferred until the circulating CD4⁺ T-cell counts recover to levels greater than 200 cells·μL⁻¹ in the blood following initiation of ART [102]. Because HIV-infected persons are at greater risk at developing influenza-associated pneumococcal co-infection, it has been proposed that the influenza vaccination be prioritised in the setting of HIV infection [19].

Unlike children, routine immunisation of HIV-infected adults with *H. influenzae* type B conjugate vaccine is not routinely recommended with the exception of those who acquire splenic dysfunction [107].

Potential future developments with respect to both pneumococcal and *H. influenzae* immunisation programmes include the acquisition of novel vaccines based on highly conserved surface proteins [2].

Conclusion

Despite significant advances in diagnosis, therapy and immunoprophylaxis, bacterial CAP remains a significant cause of morbidity and mortality in both HIV-infected and -uninfected individuals. While many of the risk factors are difficult to avoid, the smoking habit is a notable exception, especially in the setting of HIV infection, underscoring the necessity for more effective anti-smoking strategies. In the case of the pneumococcus and nontypeable *H. influenzae*, possible future innovations include the acquisition of novel protein-based vaccines, which in the case of the former, are expected to provide broad, serotype-independent protection.

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Tuberculosis

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TB/HIV co-infection represents a relevant clinical and public health issue. It is estimated that 1.1 million individuals are TB/HIV co-infected. The majority (~75%) of these patients live in Africa. The annual mortality is estimated to be higher than 300 000 patients. Although a general decrease of the mortality rate has been recorded worldwide, there are several geographical areas where it is highest, particularly in low-income countries. HIV infection is one of the most important risk factors for the development of TB disease: the qualitative and/or quantitative impairment of the immune system caused by the HIV favour mycobacterial replication. TB treatment should be administered early after the diagnosis of the disease. ART should be prescribed within 14 days after the administration of the anti-TB drugs. Several drug–drug interactions have been described, particularly in the case of induction/inhibition of the hepatic cytochromes.

TB, malaria and HIV/AIDS are the three most important infectious diseases worldwide [1]. In recent decades, the clinical burden associated with their global spread has been impressive. On the basis of their epidemiology and, in particular, their direct or indirect infectiousness, the impact on the public health scenario is dramatic.

One of the most striking epidemiological features of the last two decades is co-infection with TB and HIV [2, 3]. The geographical distribution of TB/HIV co-infection is heterogeneous, with some areas more significantly affected than others. In particular, low- and middle-income countries have been suffering the high prevalence of conditions predisposing to an increasing incidence of co-infected individuals [2, 4].

The epidemiological burden

Current estimates of TB epidemiological indicators point to a critical situation globally. The World Health Organization (WHO) strategies (*i.e.* DOTS (directly observed treatment, short course) and Stop TB) have significantly helped in reducing the impact of the TB-related

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public health emergency [5–7]; however, the efforts implemented have not allowed an annual TB incidence decline greater than 2% [8, 9]. Consequently, on the basis of this statistical trend, the predicted goal of TB elimination by 2050 seems unreachable.

The last WHO global report on TB estimated a global incidence of 8.6 million (95% uncertainty interval 8.3 million–9.0 million) in 2012, equal to an incidence rate of 122 cases per 100 000 population. The countries with the highest incidence rates were India, China, South Africa, Indonesia and Pakistan [2]. About 1.1 million (95% uncertainty interval 1.0 million–1.2 million) were TB/HIV co-infected individuals (13% of the total incident burden estimated in 2012). The majority of the infected patients were located in sub-Saharan Africa (75% of the total amount of the co-infected persons) (fig. 1) [2].

The change of the epidemiological scenario in the 1990s significantly modified global TB incidence: the emergence and spread of multidrug-resistant (MDR)-TB (*i.e.* TB caused by *Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampicin) and TB/HIV co-infection [2–5]. Furthermore, difficult-to-treat cases can potentially increase TB prevalence, the last estimate of which was 12 million (95% uncertainty interval 11.0 million–13.0 million) in 2012. However, this epidemiological indicator has declined approximately 37% since 1990 [2].

The mortality was estimated to be 1.3 million: 940 000 and 320 000 deaths in the HIV-negative and -positive populations, respectively. The highest figures are estimated in India and South Africa, two countries located in two of the most affected areas, south Asia and sub-Saharan Africa [2].

If the mortality rate was 13 per 100 000 population in the HIV-negative cohort, the inclusion of the HIV-positives increases the rate to 17.6 deaths per 100 000 population. Globally,

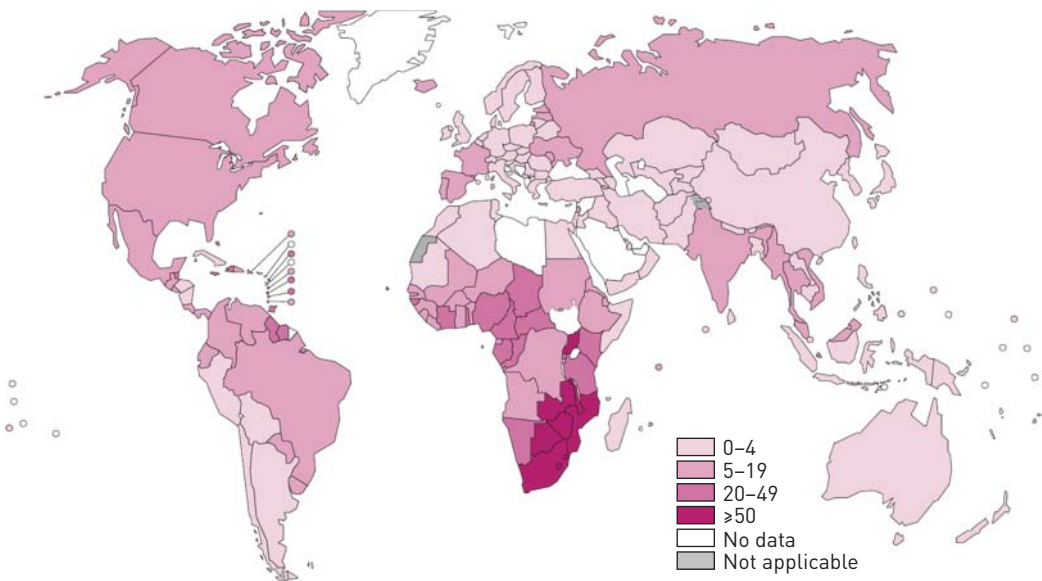


Figure 1. Estimated HIV prevalence in new TB patients in 2012. Reproduced and modified from [2] with permission from the publisher.

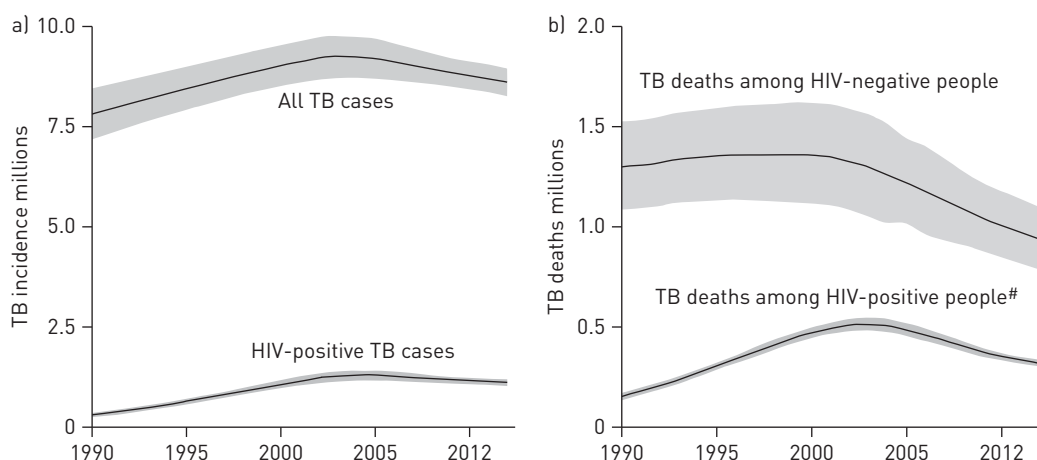


Figure 2. Estimated incidence of a) TB patients and b) deaths from 1990 to 2012. #: HIV-associated TB deaths are classified as HIV deaths according to the International Classification of Diseases (ICD-10). Reproduced and modified from [2] with permission from the publisher.

if compared with the 2003 figures, the mortality rate has declined, although with a considerable variability in countries with and without a high HIV/AIDS prevalence (fig. 2) [2].

The efficacy of anti-TB treatment has not been completely evaluated worldwide. However, 96 countries collected information for the year 2011; the treatment success in HIV-positives was 73% *versus* 87% in HIV-negatives, and in terms of poor treatment outcomes, the death rate was 19% and 3% in the HIV-positive and -negative cohort, respectively [2].

One of the most important issues is related to the underdiagnosing of the HIV-positivity status of TB patients: only 46% of individuals with TB disease (*i.e.* 2.8 million) were tested for HIV in 2012, even though the proportion is increasing year-by-year. About 37% (15 out of 41) of the high-burden countries reached an HIV testing percentage of at least 85% [2].

Other relevant advances were related to the increased proportion of TB/HIV co-infected individuals exposed to antiretroviral drugs (57%) and to TMP-SMX (80%) in 2012 [2].

cART can reduce the occurrence of TB by 65% [2, 10]. CD4⁺ cell counts represent the main criterion for the prescription of the anti-HIV drugs: the current WHO guidelines recommend the administration of ART when CD4⁺ lymphocytes are below 500 cells·μL⁻¹ [11]. However, irrespective of CD4⁺ cell counts, administration of anti-HIV drugs has to be started in cases of TB disease; the general recommendation about the administration of antiretrovirals in case of a CD4⁺ cell counts less than 500 cells·μL⁻¹ can improve the cohort of HIV-positives with a recovered immune system, who are immunologically more resistant to *M. tuberculosis* reactivation, particularly when isoniazid preventive therapy is co-administered. In TB/HIV co-infection, anti-HIV therapy should be started within 14 or 30 days according to the CD4⁺ cell count (<50 or ≥50 cells·μL⁻¹, respectively) [2, 4, 11–13].

It is estimated that the annual risk of developing TB is 5–10% when *M. tuberculosis* infection precedes the HIV infection; however, the probability of developing active TB can be higher when mycobacterial strains infect a severely immunodeficient individual [14–16].

HIV infection is considered the most important risk factor for the development of *M. tuberculosis* disease: a 20-fold increase of TB incidence has been shown in high HIV prevalence areas. GETAHUN *et al.* [17] showed that the relative risk of disease can be different according to the epidemic context: higher in low HIV/AIDS prevalence settings (*i.e.* 36.7-fold increase), lower in areas with concentrated or generalised epidemics (*i.e.* 26.7- and 20.6-fold, respectively).

The dysfunction of the innate and adaptive immunity can allow the replication of the mycobacteria in pulmonary and extrapulmonary tissues. In cases of severe immunodeficiency, the granuloma cannot be created and mycobacterial spread causes serious pulmonary tissue impairment [18, 19]. This has a clear association with CD4⁺ count decline; however, the exposure to other variables that can increase the probability of TB disease can favour a synergistic or an additional effect, independently from the severity of the immunodeficiency (*e.g.* silica dust exposure) [20, 21].

Furthermore, the HIV-related immunodeficiency impairs TB diagnosis, contributing to a healthcare diagnostic delay: patients are frequently sputum smear-negative [22]. Furthermore, the immunological tests (*i.e.* tuberculin skin test (TST) and IFN- γ release assays), performed to assess the latent infection are negative, particularly in the case of severe immunodeficiency; consequently, a proportion of patients to be treated in order to avoid the occurrence of TB disease can be missed [23].

The clinical features of TB/HIV co-infection

The clinical presentation of TB in those with HIV infection offers a number of challenges: it is more common and may be more severe, yet symptoms are often nonspecific and many investigations have less diagnostic sensitivity (table 1). HIV infection is associated with a greater than 20-fold increase in risk of TB [24]. This impairment begins soon after HIV

Table 1. Clinical features of TB

	HIV uninfected	HIV infected	
		Blood CD4 ⁺ count >200 cells· μ L ⁻¹	Blood CD4 ⁺ count <200 cells· μ L ⁻¹
Symptoms	Focal features (<i>e.g.</i> cough) predominate	Focal features plus systemic symptoms often present	Nonspecific/systemic symptoms predominate
Site of disease	Predominantly pulmonary	Predominantly pulmonary with increasing extrapulmonary disease	High rates of extrapulmonary and disseminated disease
Chest radiography	Typical findings	Typical findings	Nonspecific changes or normal
Sputum smear	Good yield	Good yield	Low yield
Mycobacterial burden (<i>e.g.</i> at biopsy)	Low	Low	High
Risk of unmasking IRIS	Minimal	Low	High
Risk of paradoxical IRIS	Low	Moderate	High

infection: in one study of South African miners, TB incidence doubled in the first year after HIV seroconversion [25].

Host immune response strongly influences the pathology of TB and the level of immunocompromise alters TB presentation [26, 27]. At blood CD4⁺ counts above 350 cells·μL⁻¹, the clinical features of TB are similar to those seen in HIV-uninfected people. However, with declining CD4⁺ counts, symptoms become less specific: there are lower rates of haemoptysis and cough may be less marked [28], and systemic symptoms of weight loss and fever often predominate (particularly in those with CD4⁺ counts under 200 cells·μL⁻¹) [29, 30]. This makes symptom screens for TB nonspecific: 62% of HIV-infected patients without TB in one South African study had at least one symptom of cough, night sweats, fever or weight loss [31]. Furthermore, a meta-analysis of symptom-based screening found that although the investigative tool (which used one or more of the following symptoms: cough, fever, weight loss or night sweats of any duration) had a sensitivity of 79%, the specificity was only 50% [32].

Although pulmonary disease remains the predominant form of TB in HIV infection, there is an increased rate of disseminated and extrapulmonary disease (which may have specific symptoms depending on the site of disease) [33]. Clinically asymptomatic or subclinical disease occurs and may represent around 20% of culture-proven, HIV-associated TB in studies from Africa and Asia [34–36]. These differences in TB presentation make the diagnosis of TB difficult and several autopsy studies have confirmed that unsuspected TB is a frequent cause of death in those with HIV infection in high TB incidence countries [37, 38].

Diagnostic investigation in TB/HIV

The altered host–microbe interaction of TB in the context of HIV infection changes the diagnostic yield of investigations. Immunocompromise results in different radiographic appearances. In those with CD4⁺ counts above 350 cells·μL⁻¹, chest radiographic changes are similar to those without HIV infection, with a predominance of upper-zone infiltrates and cavitation. This is less clear-cut in people with lower CD4⁺ counts [39]. Many different radiological patterns have been associated with TB/HIV co-infection, including lower-zone infiltrates and consolidation, and no particular radiological pattern is typical of disease [40]. A significant proportion of TB/HIV co-infected patients may have completely normal radiology [41]. It was demonstrated in a retrospective US study that the main determinant of radiographic appearance of pulmonary lesions in HIV-infected subjects is impaired immunity rather than recent infection and its progression to disease [42].

Individuals with profound immunocompromise are unable to control mycobacterial replication and consequently have a greater mycobacterial burden than the immunocompetent [43]. However, the reduction in factors associated with sputum smear positivity, such as lung cavitation, mean that sputum microscopy has a significantly lower diagnostic yield in the context of HIV infection [44, 45].

Although the traditional mainstays of TB diagnostics, sputum smear and chest radiograph, are less reliable, other diagnostic interventions may be more useful in this setting. Mycobacterial blood cultures are significantly more likely to be positive in HIV infection [46, 47]. Abdominal ultrasound may detect lymphadenopathy or splenic infarcts, which can indicate TB infection [48]. Urine tests for lipoarabinomannan (a component of mycobacterial cell walls), which have a poor yield in HIV-negative TB, may have a place in those with HIV

infection, especially as the diagnostic yield is highest in those with the most severe immunocompromise, *i.e.* the group at greatest risk of TB, and in whom traditional investigations offer less value [49]. The increased availability of nucleic acid amplification-based techniques holds the promise of improvements in TB case identification [50]: an assessment of the use of the GeneXpert automated platform (Cepheid, Sunnyvale, CA, USA) to analyse sputum samples reported sensitivity of 82%, which was not significantly lower than the 90% found in those without HIV infection [51].

IRIS and TB/HIV

Return of immune responses with ART can lead to IRIS [52]. This may occur in association with a range of infectious and noninfectious pathologies, though TB is one of the most important causes. IRIS can be divided into two groups: unmasking and paradoxical reactions. In unmasking IRIS, conditions that were asymptomatic or clinically unsuspected at the initiation of ART become apparent once immune reconstitution occurs. This may result in significant deterioration or death [53]. Although intensive screening for TB prior to ART initiation can reduce the incidence of unmasking IRIS, the limitations of the available diagnostic investigations mean that it will continue to present a significant problem (table 1) [4].

“Paradoxical IRIS” refers to the recrudescence of clinical symptoms associated with current or previously treated disease following the initiation of ART. This typically manifests as a patient who develops worsening symptoms after starting ART, having improved with TB treatment. These phenomena are presumed to result from enhanced immune activation to mycobacterial antigens and may occur at sites distant from the original disease. Given that this is not driven by viable mycobacteria (unlike unmasking IRIS), corticosteroids may be used to suppress these reactions (although many are self-limiting) [54].

In summary, while HIV infection promotes the development of active TB, the clinical features may be atypical or nonspecific. Combined with the wide range of infectious and noncommunicable disease that can occur in HIV-infected individuals (which often share clinical features with TB), this can present difficult decisions to clinicians and health services, particularly in the resource-limited environments where the majority of TB/HIV co-infection occurs.

Therapeutic issues and pharmacological interactions

HIV infection increases the risk of poor TB treatment outcome by at least doubling the death rate [55]. Excessive risk of death in co-infected patients may have several determinants, but randomised clinical trials show that adding ART to TB treatment improves treatment outcome and reduces mortality [12, 13, 56, 57]. The benefits of ART extend to patients with MDR-TB and HIV co-infection [58].

TB treatment should be started as soon as the disease is diagnosed [2, 59], following the same guiding principles as for HIV-uninfected patients. A rifamycin-based regimen is the mainstay of anti-TB treatment in patients with dual TB/HIV disease as rifamycin-lacking regimens have significantly higher failure/relapse rates (11.7% *versus* 6%; $p=0.002$) [60] and would require a substantially longer treatment duration (12–18 months). Some evidence suggests that extending treatment duration to ≥ 8 months might improve outcomes in co-infected patients [61] but this requires further observations.

ART should be initiated as soon as possible after TB treatment: most patients benefit from starting ART within 2 weeks after anti-TB therapy, though the benefit is larger in those with severe immune suppression (e.g. $CD4^+$ cell counts $<50 \text{ cells} \cdot \mu\text{L}^{-1}$) [13, 57]. The US ART guidelines state that in patients with $CD4^+$ counts above $50 \text{ cells} \cdot \mu\text{L}^{-1}$, ART should be initiated within 2–12 weeks of starting TB treatment [59]. For the small fraction of patients developing TB at high $CD4^+$ cell counts (e.g. $>220 \text{ cells} \cdot \mu\text{L}^{-1}$), an early start of treatment may not bring substantial gains [62]. In general, considering the challenges of timely determination of $CD4^+$ cell counts, current recommendations to treat TB and HIV concomitantly and to start ART as early as possible hold true [2, 59, 63].

As far as the efficacy of HIV treatment is concerned, a recent systematic review and meta-analysis showed that the probability of virological suppression and the extent of the immune recovery are similar in patients receiving concomitant TB and HIV treatment and those not receiving TB treatment [64].

In reality, only 57% of notified TB patients in 2012 who had a documented positive HIV test result started ART globally [11]. Clinicians' decisions to delay ART are probably associated with concerns over well-described drug–drug interactions between antiretroviral and anti-TB drugs, overlapping toxicity, and the risk of eliciting the IRIS [65, 66].

The rifamycins interact with several antiretroviral drugs. The former are potent inducers of cytochrome P450 (CYP) pathway, leading to subtherapeutic plasma concentrations of some classes of antiretrovirals. Moreover, rifampicin induces the uridine diphosphate glucuronyl transferase 1A1 enzymes and interferes with the integrase inhibitors that are metabolised by this metabolic pathway. Finally, rifampicin induces the ATP binding cassette transporter permeability glycoprotein, which may also lead to decreased bioavailability of concomitantly administered antiretrovirals. Rifabutin concentrations are affected by the antiretrovirals that induce or inhibit CYP enzymes.

NRTI drugs can be used as the backbone of any HIV regimen while treating patients with dual TB/HIV disease and no dose modification is required [59], but regimens composed entirely of NRTIs are less effective than combinations of two classes of antiretroviral drugs. Companion drugs of alternative classes must be used but the choice is problematic. Based on pharmacokinetic studies and a substantial number of clinical studies, efavirenz is the antiretroviral drug of choice to be used with a rifampicin-based anti-TB regimen [11, 59, 63, 67]. The dose of efavirenz is 600 mg once daily, although efavirenz 800 mg may also be used in persons weighing $>50 \text{ kg}$ [59] or $>60 \text{ kg}$ [68].

Combined treatment of TB/HIV is challenging in co-infected patients who cannot receive efavirenz due to intolerance or resistance (e.g. are on second-line HIV treatment regimens). This situation is already common in countries in the northern hemisphere and is expected to become common in resource-constrained settings as well, following more extensive virological monitoring of treated patients, as promoted by the 2013 WHO guidelines for consolidated ART [11].

Nevirapine is a widely used first-line antiretroviral but clinical studies on nevirapine-based ART for patients with dual TB/HIV disease gave inconsistent results. A recent systematic review and meta-analysis showed that efavirenz-based ART was associated with more satisfactory virological outcomes, although nevirapine-based ART could be considered an acceptable alternative whenever efavirenz cannot be administered [69].

Globally, the vast majority of persons living with HIV who are on second-line antiretrovirals are on a protease inhibitor-based regimen, mainly lopinavir/ritonavir; in more affluent countries, however, second-line ART may include any other available class of antiretroviral. Rifampicin should not be administered with protease inhibitors, whether boosted or not, at standard doses [70–73]. The use of super-boosted protease inhibitors (*e.g.* lopinavir/ritonavir 800/200 mg twice a day or 400/400 mg twice a day) is hampered by the evidence of very poor tolerability [74–77].

Rifabutin is the preferred rifamycin to use in HIV-infected patients on a protease inhibitor-based regimen because the risk of substantial drug interactions with protease inhibitors is lower with rifabutin than with rifampicin [78, 79] and a rifabutin-based regimen is equally effective as a rifampicin-based regimen [80–82]. No dose adjustment of the protease inhibitor is necessary but the dose of rifabutin needs to be reduced to 150 mg daily [83]. Data from clinical trials of patients taking rifabutin 150 mg in combination with protease inhibitors are scant; however, patients using this combination treatment should be monitored for rifabutin-related toxicity [78]. Optimal treatment regimens for TB/HIV co-infected patients are even more problematic whenever efavirenz cannot be used and rifabutin is not available. A recently published, small-scale randomised clinical trial suggests that raltegravir 400 mg twice daily might be used in association with rifampicin for the treatment of patients co-infected with HIV and TB [84]. There are no limitations for the use of enfuvirtide in association with any anti-TB drug [85] but this drug is not preferable due to its parenteral administration. Concerning newer HIV drugs, rifampicin is contraindicated in association with the NNRTIs rilpivirine and etravirine [59, 86, 87], and the CCR5 inhibitor maraviroc at standard dose [88]. No data are available on the association between rifampicin and the new integrase inhibitor cobicistat-boosted elvitegravir, while some preliminary encouraging results are available from pharmacokinetic studies on the association with dolutegravir [89].

There are several grey areas in the optimisation of combined TB/HIV treatment. Pharmacokinetic studies are becoming common but clinical trials remain rare in this field. Rifapentine, a very attractive rifamycin for the treatment of active TB and of latent TB infection (LTBI), is currently banned in international recommendations for TB/HIV therapy. Clinical trials are urgently needed if the potential of this drug is to be fully exploited. More data are needed from special populations. Treatment of dual disease in children is hampered by the lack of paediatric formulations and dosing guidelines for rifabutin, while an NNRTI-based therapy is not recommended as preferred therapy for perinatally infected infants under the age of 1 year [2]. Super-boosted lopinavir treatment in association with rifampicin is an attractive option in this population [90–93] but more evidence is needed. Data are lacking for pregnant females as well. Moreover, information on the interaction between second-line TB drugs and antiretrovirals is scant. Although fewer interactions are expected once rifamycins are no longer used, clinical trials of the new drugs bedaquiline and delamanid in people living with HIV are urgently needed. Finally, the role of therapeutic drug monitoring (TDM) for the combined treatment of dual TB/HIV diseases is poorly defined. Despite being very useful for the management of individual cases, TDM would hardly fit the public health approach to the management of ART in resource-limited settings.

Isoniazid preventive therapy in HIV-infected subjects

Given that HIV-positive individuals with latent TB are at increased risk of developing active TB, prophylaxis has been advocated in the prevention of active disease [94]. Effective regimens include isoniazid alone, dual therapy with isoniazid plus rifampicin or rifampicin

plus pyrazinamide, and triple therapy with isoniazid, rifampicin and pyrazinamide [95]. Rifampicin monotherapy has not been studied in this patient population.

Isoniazid

In 2010, a Cochrane review was published, including 12 controlled trials conducted among 8578 HIV-infected patients in both resource-limited and resource-rich settings [95]. TB preventive therapy with any anti-TB drug *versus* placebo was found to be associated with a statistically significant 32% lower incidence of active TB. All drug regimens, regardless of type, frequency or duration of treatment, were shown to reduce the incidence of active TB. These data have been subsequently confirmed by a clinical trial that randomly assigned 1995 HIV-infected patients, with or without documented LTBI, to 6 months of daily isoniazid followed by extended isoniazid or extended placebo for 30 months [96]. This trial reported an incidence of active TB that was significantly lower in the extended isoniazid group compared with the extended placebo group.

Interesting results on treatment of LTBI are those from coming from areas where both HIV and TB are endemic. In a cluster randomised controlled trial including 80 000 employees in 15 randomised mine shafts who received either standard care or enhanced TB mobilisation and screening and access to 9-month isoniazid preventive therapy (IPT) [97]. IPT was associated with no apparent benefit, although less than half of the intervention group continued isoniazid for at least 6 months and only one-third continued isoniazid for all 9 months. Failure to obtain a population effect was attributed to a high rate of nonadherence to IPT. In subgroup analysis, participants who actually took isoniazid were relatively protected during treatment, although such protection disappeared rapidly during the follow-up period. Given these findings, it has been suggested that long-term preventive treatment may be more effective than standard treatment for LTBI in areas where HIV is prevalent and TB incidence is extremely high.

Isoniazid plus rifampicin

Isoniazid plus rifampicin has also been found to significantly reduce the TB risk and death among HIV-infected individuals [95]. Equivalent efficacy was observed between isoniazid for 6–12 months and isoniazid plus rifampicin for 3 months but adverse events leading to treatment termination were more frequent among those receiving isoniazid/rifampicin combination, although this was not statistically significant. In a clinical trial of 7731 patients with LTBI, once-weekly isoniazid plus rifapentine, given under direct observation for 12 weeks, was found to be equivalent in efficacy to isoniazid monotherapy self-administered daily for 9 months [98]. Only 3% of the study population were HIV infected and randomisation was not stratified by HIV status, so there was some imbalance in the number of HIV-infected patients allocated to each treatment: 87 were assigned to the dual-therapy arm compared while 74 were assigned to the isoniazid arm. In 2011, the US Centers for Disease Control and Prevention suggested that weekly isoniazid plus rifapentine given under direct observation for 12 weeks is an alternative therapeutic option for the treatment of LTBI among HIV-infected patients who do not require HIV therapy [99]. No randomised, controlled trial has been published on the use of rifampicin alone in predominantly HIV-infected persons perhaps because of concern for acquired rifampicin resistance [95]. There are extremely scant data from clinical trials or observational studies to inform decisions and the choice of regimen for preventive treatment of HIV-infected close contacts of individuals with MDR-TB.

Therapy in TST-positive patients

A relevant point raised by the Cochrane review was that the benefit of preventive therapy seems to be restricted to those with a documented positive TST. Among patients who were TST positive, therapy reduced the risk of active TB by 62%, while therapy did not reduce the risk of active TB in patients with a negative TST [95]. These data are consistent with those reported in a review of studies enrolling both HIV-negative and -positive subjects showing a positive association between TST reactivity and incidence of TB [100]. The effect of TST positivity has been also reported in a recent randomised trial recently conducted in Botswana [96]. A 43% reduction in TB incidence was detected among those receiving 36 months of isoniazid compared with 6 months and participants whose TST showed 5 mm induration at enrolment received a substantial benefit from continuous isoniazid treatment, whereas the effect in participants who were TST negative was low and not significant.

Impact on mortality

The Cochrane review showed that although there was reduction in mortality with isoniazid monotherapy *versus* placebo among individuals with a positive TST and with isoniazid plus rifampicin *versus* placebo regardless of TST status; overall, there was no evidence that TB preventive therapy reduced all-cause mortality compared with placebo [95]. This result may be the consequence of the inclusion of TST-negative subjects, who did not receive any protective advantages from the preventive therapy. Finally, compared with isoniazid monotherapy, short-course multidrug regimens were much more likely to require discontinuation of treatment due to adverse effects.

LTBI treatment and ART

A special attention should also been directed toward the role of ART. The effect of IPT in a study performed in Botswana was independent of and additive to the TB-preventive effect of ART [96]. By study completion, 47% of the participants had initiated ART. Regardless of TST status, TB incidence was reduced by 50% in those receiving 360 days of ART compared with participants receiving no ART. In those on continuous isoniazid who also received ART, the reduction was 96%. A recent systematic review reports an overall hazard ratio of only 0.35 in persons with HIV and on ART while living in developing countries [10]. Another such review found that, even throughout ART and despite achievement of high CD4⁺ cell counts, TB incidence remains over four-fold greater than in persons without HIV [101]. A recent trial of IPT given for 12 months to persons with HIV who were on or beginning ART in Cape Town, South Africa, reported a 37% reduction in hazard of TB; most of the reduction appeared to occur during the active isoniazid treatment period and diminished during later follow-up, and there was no significant mortality benefit [102]. Further, TB preventive therapy does not appear to prevent death among persons with HIV who are TST-negative, in contrast to earlier speculation that many such persons might be TB infected but anergic due to advanced HIV disease.

Duration of therapy

The optimal duration of isoniazid for the prevention of TB in HIV-infected individuals remains unclear. Among HIV-infected patients with LTBI, clinical trials have evaluated courses of therapy ranging from 6 months of isoniazid to 6 years [95]. Long-term follow-up studies suggested that the protection of 6–12 months of isoniazid treatment in HIV-infected

persons could be short-lasting (1–2.5 years) [103, 104]. In a systematic review of 13 studies, there was no significant increase in risk for the emergence of bacillary resistance between the isoniazid arms and the placebo/no-treatment arms [105]. Results were similar when studies of non-HIV-infected and HIV-infected persons were considered separately. Because of incomplete testing and small numbers of resistant isolates, however, a modest increase in risk could not be excluded.

Public health interventions

WHO suggested a strict cooperation and joint collaborative activities between HIV/AIDS and TB programmes (table 2) [106, 107]. The main scope of the cooperation is the early diagnosis of contagious TB patients in order to avoid further *M. tuberculosis* transmission in the community, particularly in geographical areas where the HIV/AIDS prevalence is high.

The WHO document “Interim policy on collaborative TB/HIV activities” [106] points out three relevant strategic activities: 1) organisation of health services aimed at the adequate management of the TB/HIV co-infection; 2) organisation of HIV services to reduce the TB burden, particularly administering antiretroviral drugs, prescribing IPT, performing intensified case-finding and implementing infection control measures (the last three interventions are the so-called Three Is); and 3) organisation of TB services to rapidly identify HIV-positive patients. One of the first interventions to be implemented was the creation of coordinating bodies (national, regional and peripheral level) for TB/HIV activities, in order to ensure governance of the health priorities and of human/economic resources, communication between the two programmes and the involvement of all the stakeholders, particularly those not directly working in the public healthcare facilities (social/community workers, private sector, patients’ representatives, etc.).

To better allocate the financial resources it is crucial to assess the clinical burden of TB/HIV co-infection: a surveillance system collecting all HIV-related information in TB patients represents the ideal solution. All TB patients should be offered HIV testing. Furthermore, intensified active TB case-finding should be implemented in HIV-positives; early detection of TB symptoms and clinical signs is vital to improve prognosis and reduce the transmission of *M. tuberculosis* strains to close contacts and in the community.

However, the cross-sectional or prospective activities focused on the assessment of the prevalent and incident cases are not sufficient: only a monitoring and evaluation system of

Table 2. World Health Organization Stop TB Strategy

1	Pursue high-quality DOTS expansion and enhancement
2	Address TB/HIV co-infection, multidrug-resistant TB, and the needs of poor and vulnerable populations
3	Contribute to health system strengthening
4	Engage all care providers
5	Empower people with TB and communities through partnership
6	Enable and promote research

DOTS: directly observed treatment, short course. Reproduced and modified from [2] with permission from the publisher.

the joint TB/HIV activities can provide an immediate feedback to those involved in the planning activities and in the distribution of the resources. The protection of the HIV-positive individuals should be favoured, not only identifying the source of infection but even increasing the safety of the exposed host; infection control should be implemented in healthcare and congregate settings with proper administrative, environmental and personal protective measures (e.g. respirators for the exposed persons and surgical masks for the contagious patients). The morbidity rate of TB/HIV co-infected patients should be decreased by prescribing co-trimoxazole preventive therapy, which can reduce the incidence of bacterial and parasitic infections.

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Nontuberculous mycobacterial pulmonary infections

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Pulmonary nontuberculous mycobacteria (NTMs) occur in HIV patients when HIV is not well controlled and CD4⁺ T-cell counts are low. Current ART has changed the disease to the point that lung opportunistic infections are only seen in HIV patients who are not on therapy. The most common NTMs producing lung disease are *Mycobacterium avium* complex and *Mycobacterium kansasii*. As NTMs are environmental pathogens that colonise the airway, the differentiation between colonisation and infection is challenging. To address these challenges, we describe a diagnostic algorithm. Current recommendations for therapy of NTMs in HIV patients are based primarily on expert opinion. Therapy should include more than one antimicrobial from the several drugs currently recommended for the NTMs isolated from the patient. Consideration should be given to drug interactions, toxicity and level of immunosuppression. Due to the lack of correlation between *in vitro* and *in vivo* activity, a close clinical follow-up is needed to evaluate response and determine whether therapy should be modified.

A large number of diverse acid-fast bacteria that are frequently found in the environment are categorised under the term “nontuberculous mycobacteria” (NTMs). Other terms used in the literature to refer to these organisms include “mycobacteria other than TB”, “atypical mycobacteria” or “environmental mycobacteria”. The potential for these organisms to be highly pathogenic to patients with immunodeficiency became evident with the global epidemic of *Mycobacterium avium* complex (MAC), including *M. avium* and *Mycobacterium intracellulare*, causing disseminated disease in HIV patients.

The initial classification of these organisms, based on their growth rate and pigmentation, has advanced to a gene-based methodology, primarily using sequencing of the 16S ribosomal RNA (rRNA). This gene is highly conserved, allowing identification of a new class with a difference in the sequence of just 1% of closely related species. Due to this new technology, today >150 species of NTM have been identified [1]. The clinician should consider that several of these new species causing pulmonary disease might not represent a new clinical entity. For example, based on standard biochemical analysis, the laboratory can identify MAC as the aetiology of pulmonary disease in a patient with HIV. In the same patient, by 16S rRNA sequencing, the identified organism may be closely related to MAC, such as *Mycobacterium triplex*. The same patient, with the same disease, now has a new pathogen that is only minimally genetically different to MAC. The implication of this new

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microbiological information in the clinical management of HIV patient with pulmonary disease is still unclear.

Pulmonary NTM in HIV patients is caused primarily by MAC followed by *Mycobacterium kansasii* [2]. A TB-like pulmonary disease can occur in HIV patients due primarily to *M. kansasii* infection. Other NTMs reported in the literature to cause pulmonary disease in HIV patients are *Mycobacterium xenopi*, *Mycobacterium simiae*, *Mycobacterium szulgai*, and the rapidly growing *Mycobacterium fortuitum*, *Mycobacterium chelonae* and *Mycobacterium abscessus*. The risk of pulmonary disease due to NTM in this population is related to the grade of immunosuppression.

In this chapter, we will review the current understanding of the microbiology of NTMs, the host response to NTM pulmonary infection, the challenges of clinical diagnosis of pulmonary disease produced by these organisms and current antimicrobial strategies. All these topics will be addressed in the context of HIV pulmonary disease.

Microbiology of NTMs

Unlike those of *Mycobacterium tuberculosis*, NTM infections are not reportable diseases, which makes determination of prevalence and incidence a difficult process. Published data show that prevalence of NTM pulmonary infection in the USA is increasing [3–6]. The prevalence of pulmonary TB decreased from seven to five patients per 100 000 from 1997 until 2007. The prevalence of pulmonary NTM increased from 20 to 47 patients per 100 000 from 1997 until 2007. Noteworthy is that pulmonary NTM prevalence significantly exceeds that of *M. tuberculosis* [6].

NTMs have been found in different environmental sources, including soil, animals, water (treated or untreated), water distribution systems and household water plumbing [7]. MAC is ubiquitous in the environment. It can be found in water and soil. Infection is thought to occur through inhalation or ingestion. Human-to-human transmission does not seem to occur and there is no need to isolate hospitalised patients. The environmental source of *M. kansasii* is not certain, but it is possibly found in water. Person-to-person transmission has not been reported. *M. xenopi* is found in water, specially hot water, tap-water systems and showerheads. *M. simiae* was originally thought to be only environmental contamination. It is found in water. Rapidly growing mycobacteria are found in water, soil and dust, on terrestrial and aquatic animals, and in contaminated reagents and pharmaceuticals. Direct or indirect person-to-person transmission has been reported for *M. abscessus* [8].

In 1959, Ernest Runyon established a possible classification for NTMs [9, 10]. Based on the time they take to grow in media, NTM can be grouped as: 1) slow-growing mycobacteria, which take several weeks to grow in the laboratory; or 2) rapidly growing mycobacteria, which can grow in a matter of days to weeks. Based on the production of pigment, NTMs can be grouped as: 1) photochromogens, which develop pigments in or after being exposed to light; 2) scotochromogens, which develop pigment in darkness; or 3) non-chromogens, which do not produce pigment. [Table 1](#) shows the different NTMs organised into this classification.

Based on virulence factors and their pathogenicity, mycobacteria can also be ranked from always pathogenic to rarely pathogenic, as follows: *M. tuberculosis*, *M. kansasii*, *M. abscessus*, *M. intracellulare*, *M. avium*, *M. xenopi*, *M. fortuitum*, *Mycobacterium terrae*, *Mycobacterium*

Table 1. Classification of nontuberculous mycobacteria based on growth and pigmentation

Slow-growing mycobacteria

Photochromogens

Mycobacterium kansasii
Mycobacterium marinum

Scotochromogens

Mycobacterium gordonae
Mycobacterium scrofulaceum

Non-chromogens

Mycobacterium avium complex
Mycobacterium terrae complex
Mycobacterium ulcerans
Mycobacterium xenopi
Mycobacterium simiae
Mycobacterium malmoense
Mycobacterium szulgai
Mycobacterium asiaticum
Mycobacterium haemophilum

Rapidly growing mycobacteria

Non-chromogens

Mycobacterium fortuitum complex
Mycobacterium chelonae
Mycobacterium abscessus
Mycobacterium smegmatis
Mycobacterium mucogenicum

smegmatis and *Mycobacterium gordonae* [11]. Virulence varies within species and it is related, to some extent, to the following characteristics: 1) ability to form biofilms; 2) resistance to disinfectants, chemicals and topical antiseptics (particularly rapidly growing mycobacteria); 3) ability to resist opsonisation by complement; and 4) ability to survive intracellularly.

Mycobacteria have also developed the armamentarium needed to escape the host immune response. Based on prior published data, the possible mechanisms include: 1) ROS by cell wall components; 2) blockage of acidification of phagocytic vacuoles; 3) suppression of synthesis of cytokines; and 4) downregulation of lymphocyte proliferation [12–14].

Host response to NTMs

The pathogenesis of and immune response to NTMs are not completely understood. Studies evaluating these processes prior to the discovery of HIV showed that granuloma formation secondary to *M. tuberculosis* and NTM infection are pathologically undistinguishable [15, 16].

Prior lung disease is a major risk factor for the development of NTM lung infection [7, 12], including the following conditions: prior pulmonary TB, cystic fibrosis, bronchiectasis, COPD and pneumoconiosis. Altered local or systemic immune status can also predispose to pulmonary NTM infections [7, 12]; this may be caused by alcoholism, smoking, oesophageal reflux, sinus disease, immunosuppressive therapy (TNF- α inhibitors) and certain immunodeficiencies (deficit in IFN- γ production or receptor deficiency).

Advanced HIV/AIDS is usually related to disseminated NTM infection rather than lung disease [7, 12]. Nevertheless, disseminated disease is always preceded by a localised infection (gut or lungs) and bacteraemia. This cycle, if perpetuated over time, produces more bacteraemia and more tissue involvement.

The initial step is the inhalation/aspiration of the NTM with the subsequent adherence to respiratory mucosa *via* fibronectin attachment protein [7]. If NTMs survive the initial

encounter with the alveolar macrophages, other cells such as lymphocytes are called to assist. It is the interaction between the macrophage, lymphocyte and mycobacterium that leads to resolution of infection, granuloma formation or clinical disease.

Initially, the organism is engulfed by the macrophage in primary phagosomes that in turn fuse with lysosomes in the cytoplasm. Through various processes, such as production of toxic oxygen metabolites, defensins and acidification, the macrophage tries to kill the NTM. Infected macrophages respond with the production of IL-12, which activates CD4⁺ T-cells and natural killer cells.

CD4⁺ T-cells differentiate into T-helper (Th) type 1 lymphocytes, with the production of IFN- γ . This cytokine continues to activate neutrophils and macrophages with the goal of intracellular killing of NTMs. TNF- α is also secreted by activated macrophages, recruiting more Th1 lymphocytes [4, 17]. This pathway is shown in figure 1. The positive feedback cycle between IFN- γ and IL-12 is the pivotal component of the immune response to NTMs, leading to resolution of infection or granuloma formation. Development of granulomas may predispose the patient to future reactivation of NTM pulmonary disease. How frequently NTM pulmonary disease is due to reactivation rather than primary infection is still debated.

Individuals with deficiencies in components of this pathway (cytokines, receptors or cells) are more susceptible to diseases produced by intracellular pathogens such as NTMs [18]. HIV patients with lower CD4⁺ T-cell counts may produce a larger expansion of Th17 (instead of Th1) that can continually drive low-grade inflammation with the resultant of a chronic lung infection [4, 17]. This scenario is shown in figure 2.

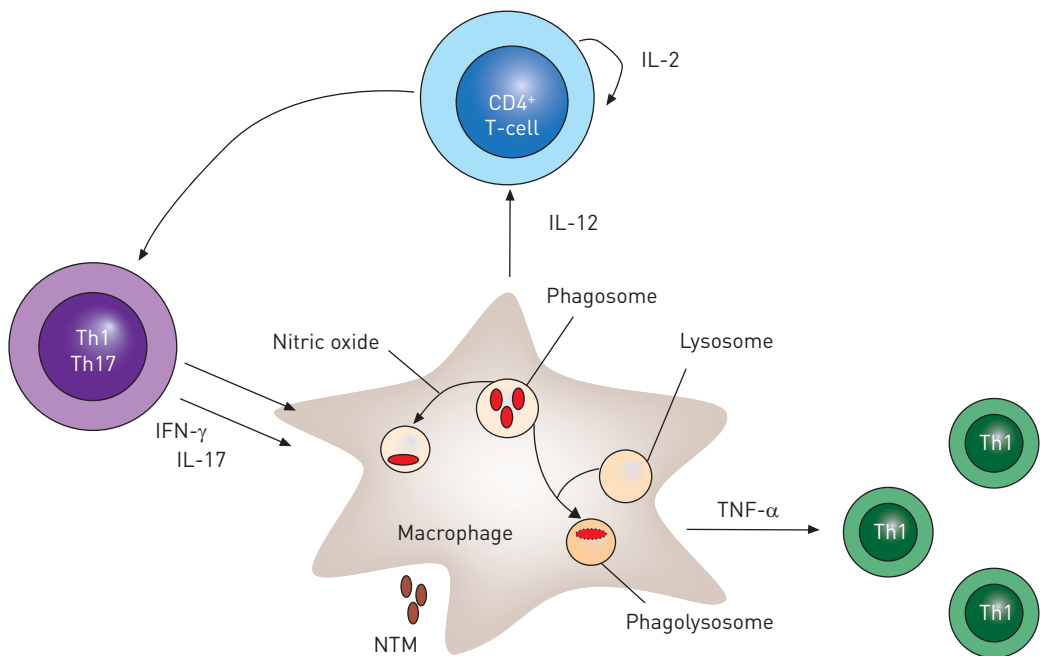


Figure 1. Host response associated with resolution of infection or nontuberculous mycobacterium (NTM) granuloma formation. Th: T-helper cell.

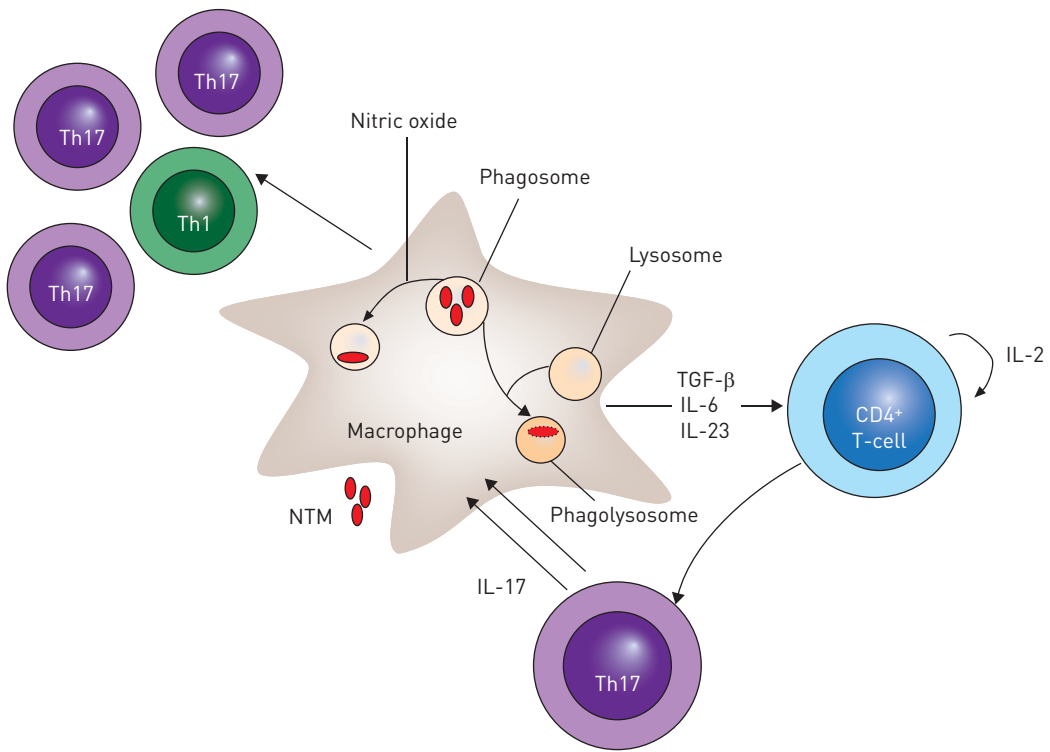


Figure 2. Host response associated with progression of nontuberculous mycobacterium (NTM) pulmonary disease. Th: T-helper cell; TGF: transforming growth factor.

Clinical diagnosis of NTM infections

One important difference in the pathogenesis of pulmonary disease due to *M. tuberculosis* versus NTMs is that once *M. tuberculosis* is able to reach the human respiratory tract, it will always cause infection, while NTMs, once in the human respiratory tract, may cause colonisation with or without infection. Because of this distinction in pathogenesis, in an HIV patient with chronic pneumonia, the isolation of *M. tuberculosis* from a single sputum sample makes the diagnosis of *M. tuberculosis* pulmonary disease definitive. However, in an HIV patient with chronic pneumonia, the isolation of NTM from sputum samples will not differentiate between NTM colonisation and active infection.

NTM colonisation of the upper respiratory tract in HIV patients may occur after drinking water contaminated with NTMs. Another possible scenario is inhalation of NTM while showering *via* aerosolisation of NTMs from the showerhead. Patients with structural lung disease, such as COPD, are at increased risk of airway colonisation with NTMs. COPD is recognised today as one of the primary lung comorbidities in HIV patients, adding to the risk of NTM colonisation in these patients.

Due to the challenges in the appropriate diagnosis of NTM pulmonary disease in HIV patients as well as patients with other comorbidities, the American Thoracic Society and the Infectious Diseases Society of America published an official statement on the subject [5]. Based on this statement, we have developed an algorithm for the diagnosis of NTM pulmonary disease in patients with HIV managed at the University of Louisville HIV

programme (Louisville, KY, USA). An outline of the algorithm is presented in [figure 3](#). For an HIV patient to be diagnosed with pulmonary disease due to NTM, three criteria should be met. First, the patient should have a clinical picture compatible with chronic pneumonia, with more than 2 weeks of respiratory complaints such as cough, sputum production, fever, night sweats or shortness of air. NTM pulmonary disease in HIV patients with advanced disease is frequently complicated with NTM extrapulmonary disease with involvement of lymph nodes, liver, bone marrow or other organs. In these patients, extrapulmonary signs and symptom are frequently present in addition to signs and symptoms of chronic pneumonia. After clinical criteria are met, the patient should have imaging studies indicative of pulmonary involvement. The most frequent findings on chest radiograph are interstitial or lobar infiltrates. Other considerations include the presence of cavitation, pulmonary nodules, hilar adenopathy or pleural effusion.

Once a patient fulfils the clinical and radiographic criteria, the microbiological criteria should be met before consideration of therapy. In [figure 3](#), two possible clinical scenarios are depicted. In the first scenario, an HIV patient has at least two respiratory samples, usually

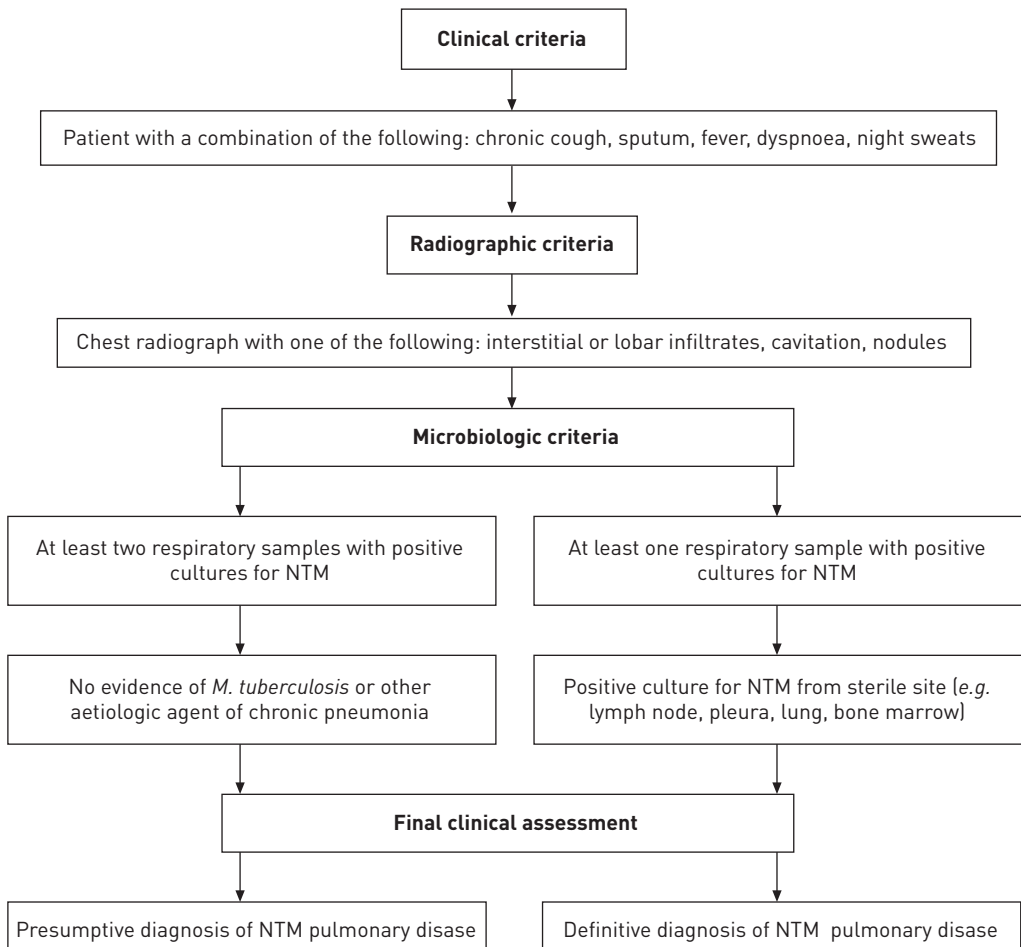


Figure 3. Diagnostic algorithm for nontuberculous mycobacterium (NTM) pulmonary disease. *M. tuberculosis*: *Mycobacterium tuberculosis*.

sputum, with positive growth of the same NTM. If there is no evidence of *M. tuberculosis* infection or another pathogen that can explain the clinical picture of chronic pneumonia, a “presumptive” diagnosis of NTM pulmonary infection will be made. Another factor to consider in these patients is the result of acid-fast smears of sputum samples. Smears are only positive in patients with a high bacterial load in the sputum. Hence, the diagnosis of NTM infection is more likely in a patient with a positive culture for NTM and a positive acid-fast smear. On the contrary, the diagnosis of NTM infection is less likely in a patient with a positive culture and a negative acid-fast smear.

A second clinical scenario depicted in [figure 3](#) includes a patient with at least one respiratory sample growing an NTM, but with a concomitant positive culture from a sterile site with the same NTM. A positive culture from a lung biopsy, hilar adenopathy or pleural fluid will confirm the diagnosis of NTM pulmonary disease. Furthermore, a positive culture from an extrapulmonary organ, such as bone marrow or liver, will confirm the diagnosis of NTM disseminated disease. These cases will fulfil the criteria for “definitive” diagnosis of NTM pulmonary disease. In these patients, therapy for NTM will be instituted even if another organism able to cause chronic pneumonia such as *M. tuberculosis* was identified, as patients with advanced HIV disease may have pulmonary infection with more than one organism.

It is important to emphasise that HIV patients with more than two respiratory samples with growth of an NTM, but without the clinical or radiographic criteria, should be considered colonised with the NTM but not infected.

Deterioration of pulmonary function with a clinical picture of pneumonia may occur in HIV patients after the start of ART. The clinical condition is called IRIS. The pulmonary deterioration in patients with IRIS is secondary to worsening of a pre-existing pulmonary infection such as a NTM infection that was clinically asymptomatic. Initiation of anti-HIV therapy is associated with improvement of T-cell function, immune recognition of the presence of mycobacteria in the lung, and the development of signs and symptoms due to the local and systemic inflammatory response. The algorithm described in [figure 3](#) can be used in HIV patients with development of pneumonia in the setting of IRIS to define the diagnosis of NTM pulmonary disease.

Treatment of NTM infection

A combination of factors makes the treatment of pulmonary disease in HIV patients with NTM infections very challenging. One consideration is that most NTMs carry multiple resistance mechanisms to common antibiotics: resistance to β -lactam antibiotics is mediated by the presence of β -lactamases; resistance to aminoglycosides is mediated by the presence of aminoglycoside phosphotransferases, acetyltransferases and efflux pumps; resistance to tetracyclines is mediated by efflux pumps; and resistance to macrolides is mediated by methylation of the 23S rRNA [19]. Another important aspect that makes the treatment of HIV patients with pulmonary NTM infections very challenging is that clinical response to therapy may not correlate to *in vitro* susceptibilities. NTMs have the ability to form biofilms in the environment and there is a strong possibility that these organisms are able to form biofilms *in vivo*. As bacteria in biofilms are in a dormant state, they are more resistant to antibiotics than their counterparts in the planktonic state. Increasing minimum inhibitory concentrations of antibiotics have been documented in bacteria located at deeper levels of biofilms. This creates the clinical challenge that susceptibility reports generated in the laboratory using the planktonic form of NTMs may not correlate with the real susceptibility

of NTMs living in biofilms in areas of necrotic lung tissue. The lack of correlation between *in vitro* and *in vivo* activity can also be due to the fact that some of the techniques to define *in vitro* susceptibilities are not completely standardised. In addition, susceptibility methodologies involve testing of single drugs, but all NTM pulmonary infections in HIV patients should be treated with multidrug regimens. Two drugs defined as resistant based on particular breakpoints may overcome resistance due to synergistic activity when used together. As in the case of *M. tuberculosis*, combination drug therapy in NTM infection is necessary to obtain synergy as well as to decrease the risk of development of drug resistance.

Considering this background regarding the current challenges for the treatment of NTM infection, a clinical approach to therapy may be: 1) to review the several drugs currently recommended for the NTM isolated from the patient; 2) to develop a multidrug regimen individualised to the patient considering factors such as drug interactions, toxicity, severity of disease and level of immunosuppression; and 3) to maintain a close clinical follow-up to define clinical response, with the understanding that drugs may need to be changed regardless of susceptibility if there is no clinical response.

The treatment of NTM pulmonary disease usually starts when an HIV patient presents with a clinical picture of chronic pneumonia and a positive acid-fast smear in sputum or another respiratory sample. In a patient like this, the primary aetiological consideration will be pulmonary disease due to *M. tuberculosis*. Other mycobacteria able to cause chronic pneumonia will be members of the NTM group such as MAC, *M. kansasii*, *M. xenopi*, *M. simiae*, *M. szulgai*, the rapidly growing *M. fortuitum* and *M. chelonae*, and *M. abscessus*. If the patient is started on empiric therapy for likely *M. tuberculosis*, that therapy may cover the possibility of infection due to some of the NTMs. *M. kansasii* is usually susceptible to isoniazid, rifampicin and pyrazinamide. *M. xenopi* is usually susceptible to isoniazid, rifampicin and ethambutol. It should be remembered that in HIV patients on ART, regimens using rifampicin should be avoided. Rifampicin will accelerate the elimination of several anti-HIV drugs, especially protease inhibitors and NNRTIs, by induction of the hepatic cytochrome P450. In addition, protease inhibitors may favour rifampicin toxicity by delaying its metabolism. In HIV patients, rifabutin is used to replace rifampicin. However, if co-administered with protease inhibitors, rifabutin dose has to be decreased by half.

The two primary NTM species causing pulmonary involvement in HIV patients are MAC and *M. kansasii*. The currently recommended antibiotics for MAC are classified as first- or second-line agents. First-line agents include clarithromycin and azithromycin. The second-line agents include ethambutol and rifabutin. Other antibiotics with *in vitro* activity against MAC include amikacin, streptomycin, ciprofloxacin and levofloxacin. In HIV patients with MAC infection, the preferred first agent is clarithromycin and the recommended second agent is ethambutol. The addition of a third drug may be considered in a patient with severe pulmonary disease or who is severely immunosuppressed.

In the case of *M. kansasii*, first-line antibiotics include isoniazid, rifampicin or rifabutin, and ethambutol. Other antibiotics with activity against *M. kansasii* include clarithromycin, azithromycin, TMP-SMX, streptomycin and quinolones.

After the patient is started on therapy, close clinical and microbiological follow-up is critical. A primary marker of drug activity will be the evaluation of sputum bacteriology. It is important to reach a culture-negative sputum, but it is also important to define the necessary time to culture negativity. As a general rule, HIV patients with NTM pulmonary disease

should be treated for 12 months after negative sputum cultures. This implies that patients with a delayed time to culture negativity will be automatically treated for prolonged durations of therapy when compared with patients with a shorter time to culture negativity. After this point, the need to continue or discontinue therapy should take into consideration the immune status of the patient. If the patient has started ART and reached a good level of immune reconstitution, therapy can be discontinued. If the patient continues to be severely immunocompromised, therapy may need to be lifelong.

Conclusion

NTM pulmonary disease in HIV patients occurs when HIV is not well controlled and CD4⁺ cell counts are low. Current ART has changed the disease to the point that these and other opportunistic lung infections are seen only in those HIV patients who are not on therapy. In this population, the most common NTMs producing lung disease are MAC and *M. kansasii*. As NTMs are environmental pathogens that may cause colonisation of the airway, the differentiation between colonisation and infection is challenging. To address these challenges, we describe a diagnostic algorithm. Current recommendations for therapy of NTM infections in HIV patients are based primarily on expert opinion. Therapy should include more than one antimicrobial from the several drugs currently recommended for the NTM isolated from the patient. Consideration should be given to drug interactions, toxicity, severity of disease and level of immunosuppression. Due to the lack of correlation between *in vitro* and *in vivo* antimicrobial activity, close clinical follow-up is needed to evaluate clinical response and determine whether therapy should be modified.

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Pneumocystis jirovecii infection

Meghan Fitzpatrick¹ and Alison Morris^{1,2}

Despite significant advances in ART and prophylactic antibiotics, PCP remains a common opportunistic infection among those with HIV, particularly among persons unaware of their HIV serostatus and in low- and middle-income countries. In high-income countries, PCP is the most common cause of respiratory failure among HIV-infected adults. Clinical, laboratory and radiographic findings in the correct clinical setting may strongly suggest the diagnosis, but confirmation of PCP requires cytological confirmation from a lower respiratory specimen. Noninvasive and non-microscopic methods of establishing the diagnosis, including PCR testing of upper respiratory samples and serum measurements of fungal elements, are active areas of investigation. The backbone of both prophylaxis and treatment of PCP remains TPM-SMX. Identifying persons with HIV and instituting appropriate ART will be key to continuing to decrease the burden of PCP.

Pneumocystis jirovecii, the hallmark pathogen of the early era of HIV/AIDS, remains a common pulmonary opportunistic infection in HIV-infected persons. Although chemoprophylaxis and effective immune reconstitution with ART have significantly reduced both the incidence and mortality of PCP, the disease still occurs, particularly in resource-poor settings. Even in high-income countries, approximately 20% of persons infected with HIV are unaware of their HIV serostatus [1] and may present to care with an opportunistic infection. PCP remains one of the leading presenting complaints of persons with a new diagnosis of AIDS. In ART-era studies from the USA and UK, PCP is the most common cause of respiratory failure among HIV-infected adults, and is frequently fatal in those who require intensive care and mechanical ventilation [2, 3].

Characteristics of the organism and its pathogenesis

Pneumocystis is a eukaryotic organism first identified over 100 years ago in rodents, where it was initially thought to be a trypanosome, then classified as a protozoan [4], before being definitively identified as a fungus in 1988 following ribosomal RNA sequencing [5, 6]. *Pneumocystis* organisms isolated from rodent and human hosts are morphologically and genetically distinct [7, 8]. The organisms are host specific, with the species infecting humans now referred to as *P. jirovecii* [6]. In the lung, *Pneumocystis* may be found in both trophic and mature cyst forms. In animal models, investigations of pathogenesis of PCP have shown

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that the trophic forms adhere to alveolar epithelial cells and result in disruption of epithelial replication [9, 10], while the cell wall components of the cyst forms provoke a robust inflammatory response mediated by neutrophils, alveolar macrophages and lymphocytes [11–14], contributing to elaboration of inflammatory cytokines and pneumonitis [15].

The transmission pattern of *Pneumocystis* in humans has yet to be confirmed but airborne transmission is supported by animal models of *Pneumocystis carinii* infection [16–18]. Direct human-to-human transmission is suggested by reports of PCP outbreaks among immunosuppressed transplant recipients, in which the outbreak strains were found to have the same genotype [19–22]. Exposure to *Pneumocystis* occurs in most people in the USA in early childhood; antibodies are detected in 75% of healthy children by the age of 4 years [23]. Reactivation of latent infection has historically been thought to be a primary mode of disease acquisition. Colonisation with *Pneumocystis* (defined as detection of the organism or its DNA in the absence of pneumonia) has been described among immunocompromised and immunocompetent children and adults (frequently those with other pulmonary disease) [24–31], suggesting that there may be a human reservoir for disease transmission.

Epidemiology

PCP was first noted as a clinical problem in Europe in the 1920s, when it was described in premature infants [32]. The subsequent history of PCP, which has been well catalogued [4], describes identification of “pneumocystosis” in other at-risk populations, including persons with severe malnutrition, those living in overcrowded conditions, those with congenital immunodeficiency, and those receiving chemotherapy or other immunosuppressive agents. Regardless, reported cases of PCP were very infrequent (less than 200 cases per year) [33] until the early 1980s, when reports of clusters of PCP and other opportunistic infections among previously healthy men heralded the arrival of HIV/AIDS [34, 35]. In the initial era of HIV in the USA, PCP was the most common AIDS-defining disease presentation and had an estimated prevalence of 75% over the course of an individual’s HIV infection [36].

Following the advent of ART in 1996, the rates of PCP in the USA and other higher-income countries dropped considerably [37]. The incidence of PCP in an HIV-infected cohort in the USA fell 21.6% per year for the first 2 years after the introduction of ART (1996–1998, overall incidence 3.4 cases per 100 person-years) [38] and similar trends were observed in London, UK (35% decrease from 4.11 per 100 person-years from 1990 to 1995, to 2.67 per 100 person-years from 1996 to 1998) [39]. A large European cohort study (EuroSIDA) described a change in rate of incident PCP from 4.9 per 100 person-years prior to 1995 to 0.3 per 100 person-years after 1998 [40]. The rate of incident PCP diagnosis as a first opportunistic infection in a cohort of US outpatients from 2003–2007 was similarly low, at 3.9 per 1000 person-years [41]. Another US study showed a rate of 8.4 per 1000 person-years from 2001 to 2008, down from 21.5 from 1996 to 2000 and 95.0 from 1993 to 1995 [42].

Despite advances in care, PCP remains the most common AIDS-defining illness in Europe [43] and in the USA it is second to only oesophageal candidiasis [41]. PCP rarely occurs in patients with a CD4⁺ cell count greater than 200 cells·μL⁻¹; a recent European study examining AIDS-defining illnesses among persons with CD4⁺ cell counts greater than 200 cells·μL⁻¹ found an incidence rate of 0.7 per 1000 person-years in this group (with the highest rate in those with CD4⁺ count 200–349 cells·μL⁻¹ and decreasing rates until a plateau of 0.1 per 1000 person-years in those with CD4⁺ counts >750 cells·μL⁻¹) [44].

PCP in low- and middle-income countries

While early studies in several African countries suggested that PCP was not prevalent in this region [45–47], current-era investigations from Africa, and other low- and middle-income countries in Asia and the Americas, report that PCP is, in fact, common [48, 49]. The initial reports of low incidence may have been secondary to differences in diagnostic testing due to availability of resources; additionally, a recent systematic review and metaregression of PCP diagnosis in tropical and low- and middle-income countries found a significant association between gross domestic product (GDP) and diagnosis of PCP. The association between PCP diagnosis and GDP was independent of diagnostic testing, implying that competing risks from pathogenic organisms that occur at higher CD4⁺ cell counts may also explain the under-representation of PCP in lower-income countries [50].

Risk factors

Among HIV-infected persons, the greatest risk factor for development of PCP is severe immunosuppression, with a CD4⁺ T-cell count <200 cells·μL⁻¹ conferring the highest risk [42, 51]. Persons who develop PCP while on ART typically have very low CD4⁺ counts which mirror the median counts among those not on ART [38, 52]. Other risk factors among persons with HIV, independent of degree of T-cell suppression, include lack of prophylaxis, homelessness [42], oral candidiasis and history of AIDS-defining illness [53]. Race has been explored as a risk factor; one US study found black race to be protective [51] while another found no relationship [53]. A recent study from Norway found a significantly lower incidence of PCP among persons from sub-Saharan Africa *versus* persons of Western descent, independent of other risk factors [54], raising the possibility of genetic contributions to host susceptibility. More recently, patient-independent risk factors for PCP have been explored; a US study reported climatological risk factors including seasonal and temperature variations as well as air pollutants and sulfur dioxide contributing to hospital admissions for PCP [55]. Similar studies have not been conducted in other geographic locations.

Presenting features

Clinical

While PCP in HIV-uninfected patients tends to present acutely, in HIV, the presentation is typically subacute. Presenting symptoms include dyspnoea (initially on exertion, progressing to dyspnoea at rest), nonproductive cough and fever. Productive cough and haemoptysis are uncommon in persons with PCP, and should prompt consideration of alternative diagnostic considerations.

Patients with PCP may be hypoxaemic at rest and are frequently hypoxaemic with activity. Lung auscultation may either be normal or may disclose fine crackles. Depending on degree of illness, tachypnoea and tachycardia may be present.

Laboratory

Laboratory findings are generally unrevealing. Lactate dehydrogenase (LDH) levels are generally elevated in association with PCP in HIV-infected persons [56, 57] but LDH levels

are nonspecific [58, 59]. Arterial blood gas will frequently demonstrate a widened alveolar–arterial oxygen tension gradient ($PA-aO_2$).

Radiographic

Plain chest radiograph

The most common appearance of an abnormal radiograph is diffuse ground-glass opacity with a perihilar distribution, which may be accompanied by a fine reticular infiltrate (fig. 1) [60, 61]. Cysts or pneumatoceles may be seen in up to 10–35% of patients with PCP, are typically multiple, upper-lobe predominant and tend to resolve with treatment [62, 63]. Pneumothoraces are more common among patients who develop cysts [62]. Even in the absence of cysts, PCP is often complicated by pneumothorax, which may occur in up to 10% of cases (fig. 2) [60, 64–66]. *Pneumocystis* is an independent risk factor for pneumothorax in patients with AIDS [65], and the combination of pneumothorax and ground-glass opacification should strongly suggest a diagnosis of PCP. Chest radiographs in HIV-infected patients with PCP may be normal [67] and lobar infiltrate is not typical of PCP.

Computed tomography

Computed tomography, particularly high-resolution computed tomography (HRCT), is useful when the chest film is subtle or unrevealing (fig. 3). Computed tomography findings most frequently include central, diffuse or mosaic ground glass (figs 3 and 4) [68, 69], areas of consolidation, or a patchy or diffuse “crazy-paving” pattern [69]. In patients with a normal chest radiograph, the presence of ground-glass opacities on HRCT is a nonspecific finding that can suggest, but not confirm, PCP, but a normal HRCT essentially rules out PCP [70].

Diagnostic testing

While physical examination features and radiographic findings may be highly suggestive of PCP, further diagnostic testing is required to establish the diagnosis, particularly due to the potential for other infectious organisms to have similar presentations.

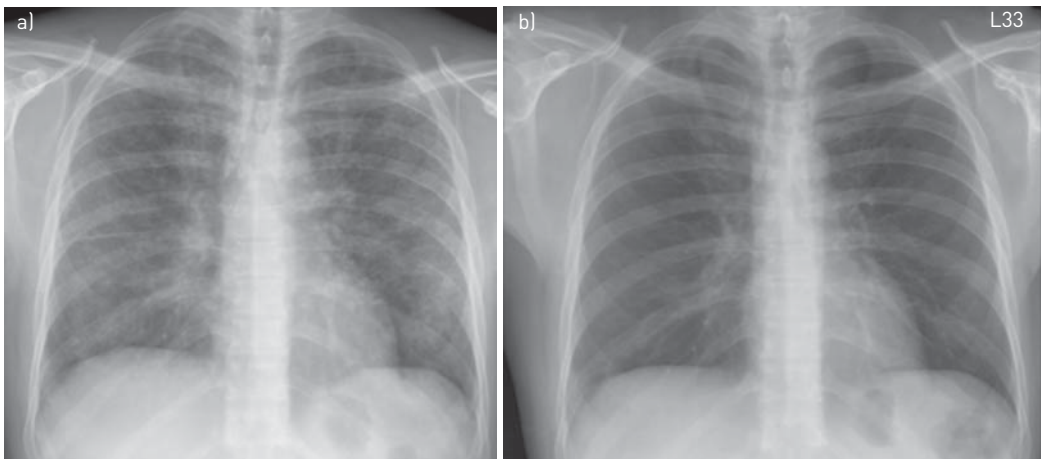


Figure 1. a) Chest radiograph of patient with PCP contrasted with b) normal radiograph obtained 5 months prior. A centrally predominant ground-glass infiltrate is present and silhouettes the previously well-defined vascular borders. Image provided by Carl Fuhrman (University of Pittsburgh, Pittsburgh, PA, USA).

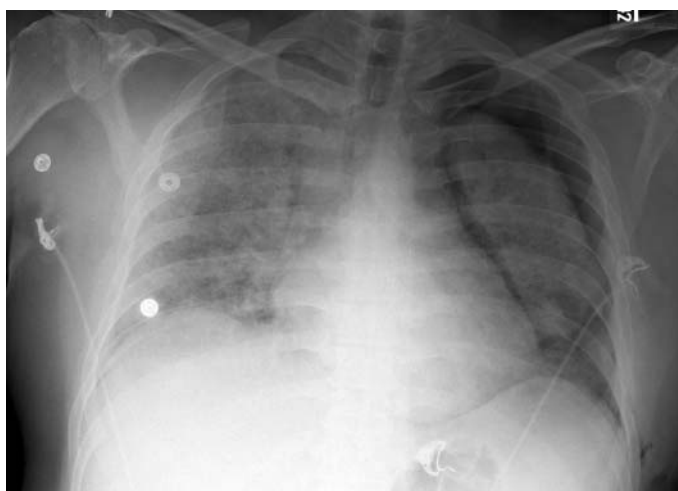


Figure 2. Chest radiograph of patient with new diagnosis of AIDS and PCP with severe diffuse ground-glass opacification and left pneumothorax. Image provided by Carl Fuhrman (University of Pittsburgh, Pittsburgh, PA, USA).

Induced sputum and bronchoalveolar lavage

As the organism cannot be reliably cultured, identification of *Pneumocystis* requires direct cytological examination. Cytological examination of the sample may be performed using Diff-Quik, methenamine silver stain, toluidine blue O stain, calcofluor white stain or direct immunofluorescent staining. Appropriate respiratory tract samples include induced sputum samples and bronchoalveolar lavage (BAL). The sensitivity and specificity of either test will depend on the degree of experience of the persons obtaining the diagnostic sample and of the interpreting laboratory, but test characteristics are more variable with induced sputum. Although the sensitivity of induced sputum samples is lower (ranging from 50% to 90%; 55.5% on average in a meta-analysis comparing with BAL [71]), this technique is less invasive

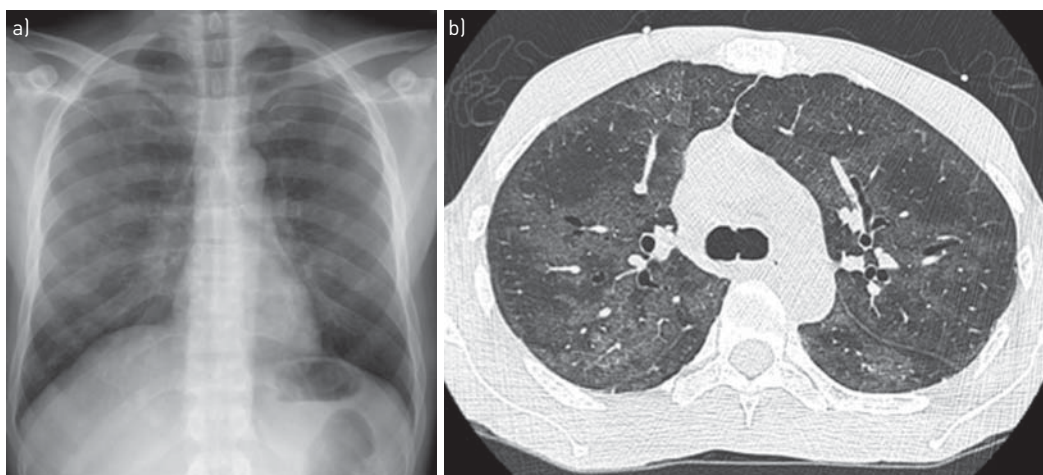


Figure 3. Subtle ground-glass infiltrate on a) chest radiograph, better visualised with b) high-resolution computed tomography performed the same day. Image provided by Carl Fuhrman (University of Pittsburgh, Pittsburgh, PA, USA).



Figure 4. High-resolution computed tomography of the chest in a patient with new diagnosis of AIDS and PCP, showing central, dense ground-glass opacification. Image provided by Carl Fuhrman (University of Pittsburgh, Pittsburgh, PA, USA).

and more readily available in resource-poor settings, where the burden of disease is the highest. Sputum induction may be performed before BAL in selected patients and settings. Patients from whom sputum cannot be induced are recommended to proceed to BAL if such testing is available. Spontaneously expectorated (non-induced) sputum is of lower diagnostic yield than induced sputum regardless of the diagnostic technique used [72] and is generally not recommended.

PCR

Noncytological methods of diagnosis are also being pursued as alternative diagnostic techniques. PCR, typically amplifying the mitochondrial large subunit or major surface glycoprotein genes of *Pneumocystis*, has been studied as an adjunct for use in upper respiratory tract specimens. These samples, including oral wash or nasopharyngeal aspirate, are easier and less costly to obtain than induced sputum or BAL, but do not carry an adequate organism burden for accurate microscopic diagnosis. PCR is very sensitive, risking overdiagnosis if used indiscriminately, as positive results may represent colonisation. A US study of quantitative PCR from oral wash of HIV-infected inpatients with suspected PCP was found to be 88% sensitive and 85% specific compared with induced sputum or BAL samples [73]. In another study, nasopharyngeal aspirate in conjunction with PCR testing for *Pneumocystis* was compared to microscopic evaluation of BAL, and was found to be 100% sensitive and 96% specific [74]. A similar study was performed in HIV-infected children in Cape Town, South Africa. PCR of nasopharyngeal aspirates compared well to PCR from lower respiratory tract samples, with 133 out of 147 samples yielding concordant results; however, many more positive results occurred with PCR than with immunofluorescence [75]. Whether these results represent enhanced detection of disease in infants and children or high false-positive rates due to colonisation is undetermined. At the current time, the use of PCR in practice is not routine but is clinically available in some centres in the USA and Europe, and remains an active area of research.

Serum $\beta(1\rightarrow3)$ -D-glucan

The best-studied circulating biomarker of *Pneumocystis* infection is serum $\beta(1\rightarrow3)$ -D-glucan, a polysaccharide component of the fungal cell wall that may be detected in the serum. β -glucan is not specific for *Pneumocystis*, and is present in the serum in the setting of other invasive fungal infections (including *Aspergillus* and *Candida*) and, possibly, bacteraemia [76]. Additionally, false-positive results may occur in the setting of β -lactam antibiotic use [77] or cellulose haemodialysis filters [78]. Many studies have been performed in HIV-infected and HIV-uninfected persons. A recent meta-analysis evaluating test characteristics across multiple studies found a pooled sensitivity of approximately 95% and a specificity of 86% [79], suggesting that the assay may be useful for ruling out PCP but is inadequate to exclude alternative diagnoses.

Management

Introduction to management

If PCP is suspected, treatment should be initiated promptly and not delayed for confirmation of the organism. Diagnostic yield is unlikely to be significantly reduced after initiation of therapy, as *Pneumocystis* may be found in the respiratory secretions of many patients even after a full course of antimicrobials [80]. The initial approach to therapy is determined based on the severity of illness, which may be generally classified as mild, moderate or severe based on degree of hypoxaemia and radiographic abnormality. Mild-to-moderate cases include patients with a $PA-aO_2$ of <35 to 45 mmHg and an arterial oxygen tension (PaO_2) >70 mmHg. Mild cases with no resting oxygen requirement and minimal or no radiographic abnormalities may be treated in the outpatient setting, using oral antibiotics. Moderate-to-severe cases, with more extensive radiographic abnormalities, resting hypoxaemia and wider $PA-aO_2$, typically require in-patient hospitalisation for the provision of supplemental oxygen and monitoring for clinical deterioration. Cases with pronounced hypoxaemia ($PA-aO_2$ >45 mmHg, PaO_2 <70 mmHg) frequently require intensive care unit (ICU) management. Severity of illness determines the route of antibiotics as well as the need for adjunctive steroids. Moderate-to-severe cases typically require intravenous antibiotics and enteral or parenteral adjunctive steroids (see later).

Antimicrobial treatment of active disease

Current guidelines for the antimicrobial treatment of PCP in HIV-infected persons from major societies in the USA and Europe [81, 82] recommend high-dose TMP-SMX as the first line of treatment. Alternative agents, which may be required in the case of a severe sulfa allergy or other contraindication, are also discussed. Antibiotic therapy should continue for 21 days.

First-line therapy of PCP

TMP-SMX (co-trimoxazole) is the current first-line treatment recommendation for PCP. Dosage is weight-based and must be adjusted for renal insufficiency. TMP-SMX is as or more effective than *i.v.* pentamidine [83–86] and has fewer treatment-limiting side-effects [86]. Side-effects of TMP-SMX include gastrointestinal symptoms (nausea/vomiting), drug eruption and neutropenia. TMP-SMX may uncommonly induce life-threatening drug reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis.

For mild-to-moderate disease, oral therapy is effective [87]. US and UK guidelines both recommend a dosing schedule of three divided doses for a total of 21 days of therapy.

For moderate-to-severe disease ($\text{PaO}_2 < 70$ mmHg), *i.v.* dosing is recommended. UK guidelines recommend a higher dose for the first 3 days of therapy, with standard dosing for the remaining 18 days. US guidelines recommend standard dosing for the total course (table 1). The route of administration may safely be changed to oral once the patient clinically improves.

Alternative agents

Alternatives are recommended in the event of true treatment-limiting effects of TMP-SMX; recommendations are similar among major guidelines (table 1). Special considerations include avoidance of primaquine or dapsone among patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Additionally, primaquine is frequently associated with methaemoglobinaemia in the absence of G6PD deficiency. Intravenous pentamidine is associated with nephrotoxicity, leukopenia and hypoglycaemia.

Sulfa resistance

Sulfa resistance has been raised as a concern, particularly because first-line prophylactic therapy, daily oral TMP-SMX, is widely used. The sulfa component of TMP-SMX inhibits the dihydropteroate synthase (DHPS) enzyme; thus, prophylactic and therapeutic regimens may generate selective pressure for DHPS genetic mutations. Such mutations have been identified at several codons in the *P. jirovecii* DHPS gene and are more common in persons with prior exposure to sulfa [88]. While some investigations have found worse outcomes or increased TMP-SMX treatment failure among persons infected with *Pneumocystis* carrying DHPS mutations [88, 89], other studies have not supported these results [90, 91], though there was a trend toward increased risk for mechanical ventilation, TMP-SMX failure and mortality in one US prospective study [92]. Further evaluation of the clinical impact of DHPS mutation is ongoing. DHPS testing is not currently recommended as part of routine clinical practice and high-dose TMP-SMX should be used even in patients who develop PCP on prophylactic doses.

Use of corticosteroids

Steroid therapy is recommended in cases of moderate-to-severe PCP ($\text{PaO}_2 < 70$ mmHg or $\text{PA-aO}_2 \geq 35$ mmHg) for suppression of the robust inflammatory response to the organism. Studies have found decreased mortality and possibly reduced risk of mechanical ventilation associated with the adjunctive use of steroids in these cases [93]. Treatment may be given as oral prednisone or prednisolone on a tapering schedule (recommended 40 mg twice daily on days 1–5, 40 mg daily on days 6–10 and 20 mg daily on days 11–21), or with equivalent doses of *i.v.* methylprednisolone if enteral absorption is inadequate [81, 82, 94]. Steroid treatment should continue for the duration of antibiotic therapy. It should be started even if the diagnosis has not yet been confirmed and can be discontinued if the patient does not have PCP.

ART initiation

The timing of initiation of ART in persons not already on ART at the time of diagnosis of PCP remains unclear. A study of multiple non-TB opportunistic infections, including PCP, demonstrated decreased AIDS progression and mortality when ART was initiated within 14 days of starting treatment for the opportunistic infection [95], and current guidelines

Table 1. Recommendations for agents and dosing schedule for treatment of PCP

	First-line treatment		Alternative treatment	
	UK	USA	UK	USA
Mild-to-moderate disease	Oral TMP-SMX: 90 mg·kg ⁻¹ ·day ⁻¹ 3 days then 90 mg·kg ⁻¹ ·day ⁻¹ for 18 days; divided three times or four times daily	Oral TMP-SMX: 15–20 mg·kg ⁻¹ ·day ⁻¹ TMP and 75–100 mg·kg ⁻¹ ·day ⁻¹ SMX; divided three times daily	Oral TMP 20 mg·kg ⁻¹ ·day ⁻¹ (divided doses) plus dapsone 100 mg daily Oral atovaquone 750 mg twice daily	Oral TMP 15 mg·kg ⁻¹ ·day ⁻¹ (divided doses) plus dapsone 100 mg daily Oral atovaquone 750 mg twice daily Oral primaquine 30 mg daily plus oral clindamycin 300 mg every 6 h or 450 mg every 8 h
Moderate-to-severe disease[#]	TMP-SMX <i>i.v.</i> : 120 mg·kg ⁻¹ ·day ⁻¹ for 3 days then 90 mg·kg ⁻¹ ·day ⁻¹ for 18 days; divided three times or four times daily	TMP-SMX <i>i.v.</i> : 15–20 mg·kg ⁻¹ ·day ⁻¹ TMP and 75–100 mg·kg ⁻¹ ·day ⁻¹ SMX; divided every 6 or 8 h	Pentamidine <i>i.v.</i> 4 mg·kg ⁻¹ daily Oral primaquine 30 mg daily plus clindamycin (600 mg <i>i.v.</i> every 6 h or 900 mg <i>i.v.</i> every 8 h, or 300 mg orally every 6 h or 450 mg orally every 8 h)	Pentamidine <i>i.v.</i> 4 mg·kg ⁻¹ daily Oral primaquine 30 mg daily plus clindamycin (600 mg <i>i.v.</i> every 6 h or 900 mg <i>i.v.</i> every 8 h, or 300 mg orally every 6 h or 450 mg orally every 8 h)

[#]: requires treatment with adjunct corticosteroids, as described in the main text. Information from [81, 82].

Table 2. Recommendations for agents and dosing schedule for primary and secondary prophylaxis of PCP

	First-line treatment		Alternative treatment	
	UK	USA	UK	USA
Oral TMP-SMX one double-strength tablet once daily Oral TMP-SMX one single-strength tablet once daily	Oral TMP-SMX one double-strength tablet once daily Oral TMP-SMX one single-strength tablet once daily	Oral TMP-SMX one double-strength tablet three times weekly Dapsone 50–200 mg orally daily (with or without pyrimethamine 50–75 mg orally weekly) Aerosolised pentamidine 300 mg every 4 weeks <i>via</i> Respigard II nebuliser [#] Atovaquone 750 mg orally twice daily	Oral TMP-SMX one double-strength tablet three times weekly Dapsone 100 mg orally daily or 50 mg orally twice daily (with or without pyrimethamine 50 mg plus folinic acid 25 mg orally weekly) Dapsone, 200 mg plus pyrimethamine 75 mg plus folinic acid 25 mg orally weekly Aerosolised pentamidine 300 mg every 4 weeks <i>via</i> Respigard II nebuliser [#] Atovaquone 1500 mg orally daily (with or without pyrimethamine 25 mg plus folinic acid 10 mg orally daily)	Oral TMP-SMX one double-strength tablet three times weekly Dapsone 100 mg orally daily or 50 mg orally twice daily (with or without pyrimethamine 50 mg plus folinic acid 25 mg orally weekly) Dapsone, 200 mg plus pyrimethamine 75 mg plus folinic acid 25 mg orally weekly Aerosolised pentamidine 300 mg every 4 weeks <i>via</i> Respigard II nebuliser [#] Atovaquone 1500 mg orally daily (with or without pyrimethamine 25 mg plus folinic acid 10 mg orally daily)

[#]: GE Healthcare (Little Chalfont, UK). Information from [81, 82].

recommend initiation of ART within this timeframe. ART may be associated with IRIS in the setting of active infection and some experts recommend withholding initiation of ART, especially in the setting of respiratory failure, until pulmonary status has stabilised to avoid worsening of acute lung injury.

Prophylaxis

Primary prophylaxis is currently recommended in all HIV-infected patients with a CD4⁺ count less than 200 cells·μL⁻¹, presence of oropharyngeal thrush, total CD4⁺ percentage <14% or any AIDS-defining illness. Primary prophylaxis may be safely discontinued when the CD4⁺ cell count recovers to greater than 200 cells·μL⁻¹ for greater than 3 months [40, 96, 97]. Secondary prophylaxis is recommended to be initiated immediately following completion of treatment for PCP and continued until the CD4⁺ count has been greater than 200 cells·μL⁻¹ for 3 months as a result of ART. Secondary prophylaxis is recommended to continue indefinitely in persons who developed PCP in the setting of a CD4⁺ count >200 cells·μL⁻¹. In resource-poor settings where CD4⁺ counts are prohibited by their cost, absolute lymphocyte count has been investigated as a surrogate of T-cell suppression. Total lymphocyte counts ranging from 1200 to 2000 cells·μL⁻¹ have been proposed as potential surrogates of a CD4⁺ count of <200 or <350 cells·μL⁻¹, depending on the setting [98–101], but these surrogates have not been validated. As in the general population, prophylaxis should be considered when HIV-infected patients require treatment with moderate dose steroids (>30 mg daily for >4 weeks) or are treated with certain other immunosuppressive agents.

Prophylactic regimens

Daily TMP-SMX is the first-line regimen for prophylaxis. TMP-SMX is preferred because of its cross-protection of toxoplasmosis and some bacteria, as well as greater effectiveness than certain alternative regimens (aerosolised pentamidine in particular) [73, 81]. The great majority of patients with non-life-threatening skin rash or hypersensitivity reaction to TMP-SMX can be safely desensitised to this medication and subsequently tolerate use [102–104]. Alternative agents for patients with severe or life-threatening reactions to TMP-SMX include dapsone (with or without pyrimethamine and folinic acid (leucovorin)), aerosolised pentamidine or atovaquone (with or without pyrimethamine and folinic acid) (table 2).

Prognosis

In the current era, prognosis for recovery from PCP is comparatively good but depends on setting of care, severity of illness, and other markers of comorbid illness or frailty. Respiratory failure and need for mechanical ventilation continue to confer the highest risk of mortality [105]. Aside from severity of respiratory disease, factors associated with mortality include variables probably representing immune status (lack of ART and low CD4⁺ count [106]), as well as low serum albumin, high serum LDH [105], anaemia and increasing age [33, 106].

In the USA, overall survival estimated from National Hospital Discharge Surveys improved significantly over time, from 21% in-hospital mortality prior to prophylaxis (1986–1989) to 16% post-prophylaxis/pre-ART (1990–1995) to 7% post-ART (1996–2005) [107]. Similar trends were seen among mechanically ventilated patients, with improvements in in-hospital mortality from 79% to 61% to 31%, respectively [107]. Survival for patients admitted to an ICU with respiratory failure due to PCP has been reported at slightly lower rates in single-centre studies, ranging from 54% to 58% [2, 3].

Conclusion

P. jirovecii remains an important opportunistic pathogen among HIV-infected persons, particularly those who are not adequately immune reconstituted with ART. Ongoing challenges include development of low-cost, noninvasive and high-yield diagnostic strategies for high-burden, lower-income countries; identifying and modifying host-independent risk factors for PCP; and further characterising features of the organism, including genetic mutations, that may confer higher risk of treatment failure. While mortality trends with effective treatment of PCP have improved over time, including for patients with higher severity of illness, the most severe cases still carry a high mortality rate. Additionally, although the incidence of PCP cases in regions with access to care has declined considerably following the introduction of chemoprophylaxis and ART, many new cases are still diagnosed, frequently in persons unaware of their HIV serostatus [33, 38], highlighting the importance of universal testing for and treatment of HIV/AIDS to avoid preventable, potentially fatal complications such as PCP.

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Viral infections

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Pulmonary infections are frequent in immunosuppressed adults and are predominantly viral. The advances in molecular diagnostic methods have increased our understanding of the role of viruses in pneumonia. Viral pneumonia is an important cause of morbidity and mortality in the immunocompromised population; however, only limited information is available concerning its impact on patients with HIV infection. In this chapter, we will review the most frequent respiratory viruses that have been implicated in viral respiratory infections and give particular attention to pneumonia in HIV-infected patients. Therefore, we will discuss the epidemiological characteristics, the clinical presentation, and the most appropriate diagnostic approaches and therapies (where available) for these viral infections.

LRTIs are a major cause of morbidity and the third leading cause of death worldwide [1]. According to the World Health Organization (WHO), in 2011 there were 3.2 million deaths worldwide due to LRTIs [2] and the cost, attributable to this entity, is an important burden on healthcare resources [3]. Respiratory viruses are considered to be the aetiological agent in almost one third of all CAP cases; in particular influenza viruses (A and B), rhinoviruses, human parainfluenza virus (HPIV)-1, HPIV-2 and HPIV-3, and coronaviruses. Globally, it is estimated that 100 million cases of viral pneumonia occur annually [4]. The improvement of molecular diagnostic techniques has demonstrated the increasing prevalence of viral pneumonia in recent years. There are few studies regarding respiratory viruses in immunocompromised patients, particularly in those with HIV, but recently viral aetiology was reported in approximately 23% of pneumonia among immunocompromised patients [5, 6]. These patients present deficiencies in humoral and cell-mediated immunity that can potentially alter the course and severity of common infections [7]. Despite ART, some HIV patients may remain at risk of morbidity associated with respiratory viral infections, especially in cases where there is impaired ability to generate antigen-specific responses [7]. Additional risk factors for respiratory infections in HIV patients are active smoking habits and chronic lung comorbidities.

The objective of this chapter is to provide a comprehensive and updated review of viral infections in HIV-infected patients. The aetiology, epidemiology, clinical presentation, diagnosis and therapy for the most common respiratory viruses causing respiratory infections in immunocompromised patients will be discussed.

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Influenza virus

Approximately 100 million cases of viral pneumonia are reported in adults annually [4]: influenza viruses (A and B), rhinoviruses, HPIV-1, -2 and -3, and coronaviruses are the main causes.

Influenza virus, which belongs to the Orthomyxoviridae family, is an RNA-virus classified as type A, B or C on the basis of major antigenic differences. These viruses are enveloped and covered by surface projections that are glycoproteins with haemagglutinin or neuraminidase activity, and are frequently changing through two different mechanisms: antigenic drift and antigenic shift.

Antigenic drift involves small, gradual changes in antibody-binding sites (haemagglutinin and neuraminidase) of a virus, which may make it resistant to antibodies formed against earlier strains; this occurs in both type A and type B viruses. Antigenic shift is an abrupt, major change that is the result of combining two or more viral strains and producing a novel influenza A virus subtype, which had not previously been circulated. It occurs only with influenza A virus because influenza A infects more hosts other than humans, and can cause a widespread and severe outbreaks or pandemics.

The high degree of viral antigenic variability is responsible for seasonal epidemics (antigenic drift), and is described for both influenza A and B. Severe outbreaks and pandemics due to antigenic shift are less frequent and occur only in influenza A virus [8].

Transmission

The influenza virus is primarily transmitted person-to-person by airborne particles, such as small droplets generated by coughing, sneezing and talking, and are projected onto mucus membranes or contaminate hands by touching the nose or mouth [9]. Generally, the incubation period is between 24 and 48 h. The viral shedding starts 5 days before the onset of symptoms in healthy adults, but its duration is longer in immunocompromised patients [10–12].

Clinical presentation

Seasonal epidemics of the influenza virus occur throughout the year in subtropical and tropical climates, and during the winter months in the Northern hemisphere; starting in late autumn, peaking in the middle of winter and ending in the late spring of the following year.

Influenza is usually self-limiting. However, severe complications, such as pneumonia, can occur, particularly in high-risk individuals such as HIV patients, and may lead to significant increases in hospitalisation and mortality rates. Nonetheless, there are few data on influenza pneumonia in HIV patients. Recent studies demonstrated that in the absence of ART, HIV patients have an increased risk of hospitalisation, death, and prolonged illness due to influenza when compared with the general population [13; 14].

The influenza pandemic of 2009–2010 (H1N1) gave us new knowledge of the influenza virus in immunocompromised patients [15–17]. The reported cases of the pandemic H1N1 influenza were mainly mild infections. In the USA, there were fewer deaths recorded during the pandemic than 1 and 3 years following the pandemic [18]. WHO estimated approximately 16 000 deaths between April 2009 and January 2010, during the pandemic. The majority of these deaths corresponded to patients with underlying risk factors, such as

metabolic dysfunctions, pregnancy, obesity and immunosuppression, which contributed to the worse outcomes [17, 19].

Several studies reported that 1–6% of patients hospitalised with H1N1 were infected with HIV [20, 21]. Reports from Africa have shown that a high proportion of fatal cases as a result of H1N1 occurred in HIV-infected individuals with advanced disease and who were not on ART [16]. Alternatively, in a study published in the USA, HIV patients with influenza experienced similar rates of intensive care unit (ICU) admission (29% *versus* 34%) and death (13% *versus* 13%) when compared with non-HIV patients [20]. ORMSBY *et al.* [22] suggested that the 2009 H1N1 infection was more severe in HIV-infected patients with late and advanced HIV disease than in well controlled patients on ART [22].

Therapy

Two groups of antiviral drugs are currently available for influenza, these are: M2 protein inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir) (table 1). M2 inhibitors are only active against influenza A, and they work by blocking the ion channels of the viral M2 protein and inhibiting its decapsulation. Resistance develops through a single nucleotide change involving the transmembrane portion of the molecule and can develop as early as 2–3 days after starting the therapy. These antivirals should be administered within 48 h of the onset of symptoms. Oral or inhaled neuraminidase inhibitors are both effective against influenza A and B. They work by blocking the surface protein neuraminidase, and trap the virus within the infected respiratory epithelium and prevent its dissemination. The rate of resistance is very low; however, some resistant cases were reported in the H1N1 pandemic [23]. In cases of severe pneumonia, medication is recommended even after 48 h from the onset of symptoms.

Prevention

Influenza A and B viral infections can be prevented by prophylactic use of neuraminidase inhibitors [24]. Due to the risk of highly morbid viral infections (immunodeficiency) and the high frequency of additional risk factors (smoking, chronic lung diseases) preventive strategies are recommended in the HIV population.

Table 1. Treatment and prevention

Respiratory virus	Treatment	Prevention
Influenza virus		
A	Oseltamivir, zanamivir, amantadine, rimantadine	Vaccines, oseltamivir, zanamivir
B	Oseltamivir, zanamivir	Vaccines, oseltamivir, zanamivir
RSV	Ribavirin	Palivizumab
Human metapneumovirus	Ribavirin	
Human parainfluenza virus	Ribavirin	
Rhinovirus	Pleconaril	IFN therapy
Adenovirus	Cidofovir, ribavirin	
CMV	Ganciclovir	
Varicella	Acyclovir, valacyclovir	Vaccine
Herpes simplex virus	Acyclovir	

Current guidelines for the prevention and treatment of opportunistic infections in HIV-infected patients recommend annual influenza vaccination in order to reduce the risk of influenza and of post-influenza bacterial pneumonia in this population [25]. In fact, the prolonged shedding, due to the continuous replication of the influenza virus, and the increased risk of complications and death in HIV patients make this population an important target for influenza vaccination campaigns.

Each seasonal vaccine should contain the most up-to-date strains predicted by the public health authorities on the basis of viral surveillance data. Trivalent influenza vaccines include two influenza A strains (A/H1N1 and A/H3N2) and one influenza B strain. Trivalent influenza vaccines provide limited or no cross-reactive protection between the two influenza B lineages. The seasonal trivalent vaccine was mismatched for the circulating influenza B lineage in five out of 10 influenza seasons between 2001 and 2010 in the USA and in four out of eight seasons between 2003 and 2010 in Europe. It was for this reason that in February 2012 WHO recommended B strains, from both lineages, to be included in the quadrivalent vaccines for 2012/2013 seasonal vaccines to be used in the Northern Hemisphere. Several studies show the superior immunogenicity of the quadrivalent vaccine for the additional B strain without interfering with immune responses to shared strains [26–29].

Alternatively, there is a discussion concerning the appropriate dose of an influenza vaccine in an HIV-patient. Some researchers have hypothesised that administering higher antigen doses of an influenza vaccine may improve immunogenicity and prevent influenza and its clinical complications in this population [30, 31]. The protective efficacy of the trivalent inactivated influenza vaccine in healthy individuals achieves 70–90% [32], while in the HIV population, it is approximately 40% with some patients not achieving a protective titre [33, 34]. The reasons for decreased antibody responses to the influenza vaccine in HIV patients are not fully understood; however, two main predictors of adequate response to influenza vaccine may be higher CD4 cell counts (≥ 200 cells· μL^{-1}) and undetectable viral loads (< 50 copies· mL^{-1}). Since HIV infection compromises CD4 populations, a reduction in the number of functional T-cells possibly entails an inadequate response to the trivalent vaccine, particularly in those with very low CD4 counts or high viral loads. However, more recent studies show that HIV patients reach higher levels of influenza seroprotection if vaccinated with the higher dose of influenza vaccine [30, 31].

Respiratory syncytial viruses

RSVs belong to the Paramyxoviridae family and are enveloped viruses with single-stranded non-segmented RNA and are classified into two antigenic groups, A (causing more severe disease) and B. Both groups can cause outbreaks and are associated with LRTIs in childhood.

Transmission

Seasonal outbreaks occur from November to April in the northern hemisphere (peaking in January or February), and from April to September in the southern hemisphere. Seasonal outbreaks often last for 4–5 months in a community [35–37]. An RSV infection is usually transmitted through direct contact with virus-containing secretions or fomites, but it can also occur through large aerosol droplets.

In the last 20 years, RSV has been identified as an important cause of pneumonia in adults, especially in the elderly, where it has become the second most frequent viral cause. Overall,

the rate of RSV as an aetiology of CAP is 2–5% throughout the year and 5–14% during winter [38–41].

Children aged less than 6 months, patients with chronic diseases (cystic fibrosis, asthma, *etc.*) or congenital heart disease, institutionalised elderly individuals and immunosuppressed patients are at risk of developing RSV pneumonia [42].

Adults with severe immunodeficiency are at a particular risk of severe RSV infection [43, 44]. Its clinical presentation in HIV patients is similar to that in non-HIV patients but its morbidity and mortality are significantly increased, the severity of the infection depending on the magnitude of the immunosuppression. The overall mortality in adults varies according to the patient's immune status, from 1% to 5% in healthy adults, to 41% in bone marrow transplant recipients [45].

Therapy

A specific antiviral therapy is always recommended in immunocompromised patients with LRTI symptoms due to high mortality risk.

Ribavirin is a nucleoside analogue that inhibits viral replication; it has been approved by the US Food and Drug Administration (FDA) for the treatment of RSV in children in its inhaled form. However, it requires a special aerolisation device for delivery and significant environmental precautions. Palivizumab is an RSV monoclonal antibody and the only FDA-approved drug for prophylaxis that has been used to treat upper respiratory tract infections and LRTIs caused by RSV in severely immunocompromised patients.

Rhinovirus

Rhinoviruses are nonenveloped, single-stranded, positive-sense RNA viruses of the genus *Enterovirus* in the Picornaviridae family. There are more than 100 different strains that are genetically divided into three classes: human rhinovirus (HRV)-A, HRV-B and HRV-C [46]. Rhinoviruses are responsible for more than a half of all common cold episodes in adults. Advances in molecular methods for diagnosis has shown that rhinoviruses may also cause pneumonia and induce asthma exacerbations [42].

In adults, approximately 5–10% of viral pneumonias are caused by a rhinovirus [47–49]. A recent study of CAP among immunocompromised patients found the rhinovirus was responsible for 12% of cases, being the most common virus isolated; the mortality rate was 18%, suggesting that it may have been an underestimated respiratory virus [6].

The combination of antiviral chemoprophylaxis and control measures, such as hand washing, would be expected to reduce the risk of LRTIs by rhinoviruses, particularly in patients with comorbidities.

Therapy

Intranasal IFN demonstrated prophylactic efficacy against a natural rhinovirus infection. However, it is not therapeutically effective in established colds caused by a rhinovirus [50].

Pleconaril is the first antiviral to be proven effective in clinical practice to reduce duration and severity of viral respiratory infection symptoms after established illness [51].

Human parainfluenza virus

HPIVs are single-stranded RNA viruses that belong to the Paramyxoviridae family. There are two genera of HPIV, *Respirovirus* (HPIV-1 and HPIV-3) and *Rubulavirus* (HPIV-2 and HPIV-4). HPIV is classified into four serotypes (HPIV-1–4), all of which can cause LRTIs in humans, such as bronchitis, asthma and pneumonia, especially in infants, young children, the elderly and immunocompromised individuals [52, 53].

HPIV-1 and HPIV-3 are among the major pathogens that cause hospitalisation for viral LRTIs throughout the world; since in adults, HPIV-1 and HPIV-3 show high prevalence and are associated with up to 12% of acute LRTIs [54, 55]. HPIV infections are generally limited to the respiratory tract and do not spread systemically, unless the infected individual is severely immunocompromised.

Transmission

Transmission can occur through direct contact with the infected host, by respiratory droplets, or fomites [56]. The nasopharynx and oropharynx are primary locations of initial HPIV replication.

Few data exist on HPIV pneumonia in patients with HIV. The study by GARBINO *et al.* [53], based on the analyses of bronchoalveolar lavage (BAL) samples by PCR techniques in HIV patients with LRTIs, showed HPIV in 5% of the samples but always in association with other pathogens (co-infection).

Therapy

Currently, there is no specific antiviral therapy for HPIV infection. Nonetheless, CHAKRABARTI *et al.* [57] reported a good response to ribavirin in HPIV respiratory infections among haematopoietic stem cell transplant recipients.

Adenovirus

Adenovirus is a DNA virus that belongs to the Adenoviridae family. There are approximately 52 serotypes, but only a few of them cause human diseases. Adenovirus infections have a worldwide distribution throughout the year.

Pulmonary infections are associated with serotypes 1–5, 7, 14 and 21. Serotype 14 is associated with severe pneumonia in susceptible adults and children (solid-organ transplant recipients, HIV patients and individuals with other forms of impaired cell immunity) [58]. There are reports concerning adenovirus-infection epidemics in closed or crowded settings (e.g. military recruits) [59–61]. Respiratory infections for adenovirus also account for 5–10% in the paediatric population and from 1% to 7% in the adult population [62].

Transmission

The dissemination of adenoviruses occurs by direct inoculation into the conjunctiva, aerosols, faeces and fomites; the virus is capable of surviving in contaminated areas of the environment for several weeks. Viral reactivation can also take place in immunosuppressed patients, resulting in several clinical syndromes [63].

Clinical presentation

Clinical presentation can range from asymptomatic viraemia to respiratory and gastrointestinal disease, haemorrhagic cystitis and severe disseminated illness. The clinical presentation is characterised by fever, cough and dyspnoea, with a mean duration of 3–5 days. Pulmonary opacities are often patchy and irregular or reticular at radiological images, but consolidations can also be observed. However, the clinical spectrum is broad and dissemination or pneumonia can be fatal, in both immunocompetent and immunocompromised patients [63].

KHOO *et al.* [64] studied adenovirus infections in patients with AIDS and found the risk of adenovirus infection to be 28% at 1 year (17% if the CD4 count was >200 cells·mm⁻³ *versus* 38% if the CD4 count was <200 cells·mm⁻³). Since the advent of ART, adenovirus infections are uncommon in HIV/AIDS patients until the deterioration of their immune system [64].

Therapy

Therapy with cidofovir has been used and several reports demonstrated the efficacy of the combined therapy cidofovir and ribavirin, especially in patients with poor clinical outcomes [63].

Human metapneumovirus

Human metapneumovirus (HMPV) infection has been detected worldwide, at any age, and in both the community or hospitalised patients, with the most severe disease reported in elderly and immunocompromised patients. This virus belongs to the same family as RSV and HPIV. It is usually acquired in early childhood and causes bronchiolitis, croup and pneumonia.

Transmission

HMPV is thought to be transmitted by direct or close contact with contaminated secretions, which may involve saliva, droplets or large particle aerosols.

Clinical presentation

Symptoms are usually very similar to those caused by RSV, with a range of illness from mild respiratory symptoms to severe bronchiolitis and pneumonia. The incubation period is approximately 5 days; the clinical picture is similar to that of other viruses, with nasal congestion, coughing, wheezing, fever and dyspnoea. Chest images show bilateral alveolar opacities in 43% of cases, and nodular opacities and pleural effusion can also emerge [65].

Therapy

There is no specific therapy for HMPV infection; however, in 2007, RAZA *et al.* [66] reported a successful ribavirin treatment in a lung transplant recipient with severe HMPV pneumonia.

Coronavirus

Coronavirus, a genus of the Coronaviridae family, are enveloped RNA viruses that are primarily associated with respiratory infection at any age worldwide and cause epidemics every 2–3 years.

Approximately 15% of common colds in adults are caused by coronavirus [67, 68]. There are five strains associated with respiratory infection in humans, these include: severe acute respiratory syndrome coronavirus SARS-CoV, a life-threatening severe acute respiratory syndrome that was identified after outbreaks of a severe respiratory disease in China during 2003 [69]; human coronavirus (HuCoV)-OC43 and HuCoV-229E, both of which are associated with common colds; HCoV-NL63 and HKU1, both of these are associated with LRTIs and were identified in the Netherlands in 2004 and in Hong Kong in 2005, respectively [70, 71].

Clinical presentation

The infections for coronavirus mainly occur in winter, with an incubation time of 2–5 days; the most common symptoms are myalgia, chills and dyspnoea, with possible progression to respiratory failure, while fever is uncommon. The radiological pattern is nonspecific, commonly characterised by diffuse pulmonary ground-glass opacities on chest tomography.

In a prospective study in Hong Kong, coronavirus was presented in 2.1% of patients hospitalised with acute respiratory illness [72]. Several studies demonstrated that coronavirus is the cause of CAP in children and adults [5, 73, 74]. Few studies exist within the HIV population; however, a study by GARBINO *et al.* [53] found respiratory viruses in 18.6% of all BAL samples taken from an HIV population (n=55), in which coronavirus OC43 was identified in three samples (27.2% of viral infections).

Therapy

No specific treatment is available for coronavirus infections; however, in cases of severe disease protease inhibitors (lopinavir and ritonavir) and IFN (α and β) can be administered [75]. There is no evidence of efficacy for ribavirin use.

CMV

CMV is a DNA virus from the Herpesviridae family whose infection is highly prevalent in the general population. CMV is a common cause of acute LRTIs, particularly in immunocompromised patients, and it is associated with a wide spectrum of diseases ranging from an asymptomatic disease or a mononucleosis-like syndrome to a severe disease in an immunocompromised host [76–78].

The principal risk factors for CMV infection include HIV infection and immunosuppression (bone marrow/stem cell transplantation and solid organ transplantation), *i.e.* conditions which are associated with significant morbidity and mortality [76–78].

CMV infection is the most common viral opportunistic infection and had a prevalence of 21–44% in the HIV population before ART became available [68]. After the resolution of acute infection, CMV establishes latent infection [68]. Most HIV patients have latent CMV infection of many tissues including the lung, and most cases of CMV pneumonia are believed to be caused by CMV reactivation due to severe immunosuppression.

Clinical presentation

Pneumonia caused by CMV is reported to be similar to PCP, with fever, cough, hypoxaemia, diffuse radiographic opacities and pleural effusion in 33% of cases [68].

SALOMON *et al.* [77] demonstrated that CD4 counts $\leq 12 \times 10^6$ cells·L⁻¹ (OR 9.2) and extra-pulmonary CMV manifestations (OR 20.4) were independently associated with CMV pneumonia.

Therapy

CMV pneumonia treatment is recommended in patients with HIV when CMV is the sole pathogen and when there is symptomatic disease; however, treatment does not result in improved survival or outcome when other pathogens are present [68]. There are currently four antiviral drugs licensed for the treatment of CMV infections: ganciclovir, valganciclovir, foscarnet and cidofovir. For the treatment of CMV pneumonia, ganciclovir is recommended with a combined high-dose immunoglobulin. However, this treatment has not been evaluated in a randomised controlled trial.

Human bocavirus

Human bocavirus was first isolated in nasopharyngeal aspirate specimens from children with LRTIs in 2005 [79]. Unlike many other respiratory viruses, it is a single-stranded DNA virus of the Parvoviridae family transmitted *via* respiratory droplets and has been detected worldwide.

In a recent study in children with CAP, 17 respiratory viruses were tested during the acute phase of the disease and bocavirus was among the most frequently detected virus after RSV and HRV [80]. In a different paediatric population from South Africa NUNES *et al.* [81] found bocavirus in 9.5% of HIV-infected and in 13.3% of HIV-uninfected children with LTRIs.

In the adult HIV series from GARBINO *et al.* [53] only one out of the 55 patients (3.1%) who underwent the BAL analysis was positive for bocavirus.

Clinical presentation

Unfortunately, clinical presentation is not well defined for bocavirus infections, but it does include fever, wheezing, LRTIs and diarrhoea.

Therapy

There is no antiviral treatment available at the present time for bocavirus.

Herpes simplex virus

Herpes simplex virus (HSV) is an enveloped, double-stranded DNA virus. There are two types, HSV-1 and HSV-2, both of which produce lifelong infection.

Transmission

Transmission is due to close contact with an infected person who is shedding the virus from their skin, saliva or in secretions from the genitals.

HSV infections (oral and genital) are frequent in HIV patients, especially in the presence of severe immunodeficiency. Herpetic pneumonia is rare in HIV patients. HSV-1 is the usual cause of these cases, pneumonia due to HSV-2 is extremely rare [82, 83].

Clinical presentation

Despite the low frequency of pulmonary infections that are HSV-mediated, sporadic cases have been reported of pneumonia and tracheitis in HIV patients [83, 84].

Therapy

For the treatment of HSV pneumonia acyclovir has demonstrated beneficial effects in several studies and the rate of resistance is minimal [85].

Varicella–zoster virus

Varicella–zoster virus (VZV) is the causative agent of varicella (also known as chickenpox) and zoster.

Transmission

VZV is primarily due to person-to-person spread of airborne respiratory secretions. Patients infected with HIV are at increased risk of VZV infections [86].

Clinical presentation

In patients with low CD4 T-cell counts, multisegmental zoster or zoster generalisatus are often observed. Cases of VZV pneumonia are very rare but patients with severe immunocompetence are at increased risk [85].

POPARA *et al.* [86], in a study in HIV patients from South Africa, showed that seven (58%) out of 12 patients who were hospitalised with chickenpox developed clinically severe pneumonia and three (43%) out of the seven died despite receiving antiviral treatment within 12 h after admission.

Therapy

The antiviral agents licensed for treatment of VZV include acyclovir, valacyclovir and famcyclovir [87].

Prevention

Varicella vaccination seems to be safe and effective for patients with a CD4 T-cell count of $>400 \text{ cells} \cdot \mu\text{L}^{-1}$ [88]. Vaccination should be considered if VZV serology is negative.

Viral–bacterial co-infection

Viral–bacterial co-infection is an important contributor to morbidity and mortality. Bacterial co-infection was frequently reported in cases of influenza pneumonia during the 2009 influenza A-H1N1 pandemic, *Streptococcus pneumoniae* being the most frequent co-pathogen [89].

Reports on specific populations, such as critically ill patients, found bacterial co-infection ranging from 18% to 33% in patients with the 2009 influenza A-H1N1 viral pneumonia [90, 91]. CILLÓNIZ *et al.* [92] found that 5.6% of ICU patients with CAP and a known

aetiology presented with viral–bacterial co-infection, the most frequent combination being the influenza virus and *S. pneumoniae* [92]. Moreover, patients with co-infection presented with more severe inflammation and clinical presentation than individuals with mono-microbial infections [92].

Similarly, a recent study involving HIV patients with CAP showed that 331 (11.5%) of presented with viral–bacterial co-infection, the most frequent combination being the influenza virus and *S. pneumoniae* [93].

The most relevant clinical implication of identifying viral–bacterial co-infection is the choice of the most appropriate antimicrobial treatment for HIV patients, due to the risk of increased severity in clinical presentation and outcomes.

Microbiological diagnosis

The benefit of a more accurate viral diagnosis is crucial because the patient can then receive an appropriate antiviral therapy [24]. In addition, early treatment may reduce: the severity and duration of symptoms, hospitalisation and complications, the extent and quantity of viral shedding, and possible mortality [94, 95].

The key to a successful diagnosis is the collection of a good quality respiratory-tract sample for laboratory testing. Specimens should be collected as soon as possible, preferably within 48 h of the onset of illness. Appropriate samples for testing respiratory viruses include nasal and oropharyngeal swabs, which are then placed in a single viral transport medium. Nasopharyngeal washes are the sample of choice for children aged less than 3 years. False-negative results can be seen from upper respiratory tract samples in patients with pneumonia; therefore, in cases where there is clinical and/or radiological evidence of lower tract involvement, BAL should be considered [96].

Microbiological diagnosis of a respiratory virus can be achieved by serology, virus culture, antigen detection and nucleic acid testing (table 2).

Serological testing

The determination of antibody titres is not recommended for diagnosis of respiratory viral infections, since it has a limited sensitivity among immunocompromised patients. The most reliable method for serological diagnosis is the demonstration of a greater than four-fold increase in virus specific IgG between paired acute- and convalescent-phase serum specimens [97]. Hence, the results are only useful for retrospective diagnosis and for epidemiological/research purposes and will not influence clinical management.

Virus isolation

Conventional culture involves the inoculation of specimen, taken from the patient, into a cell culture. Although a viral culture has been the reference technique, they have considerable limitations. Usually, it requires specific technical expertise, is labour-intensive as well as expensive, and it can take several days to grow and identify the virus. In addition, a considerable number of respiratory viruses, including rhinoviruses, HMPV, coronaviruses and human bocavirus, grow poorly or not at all in viral culture.

Nevertheless, virus isolation is usually more sensitive than antigen detection assays and it is capable of recovering novel or highly divergent strains missed by other tests, providing an isolate

Table 2. Comparison of diagnostic techniques

Diagnostic Tests	Time to results	Advantages	Disadvantages
Nucleic acid amplification test	1 h–2 days	High sensitivity and specificity Detects several respiratory viruses simultaneously using multiplex PCR technique Distinguishes influenza types and subtypes	Unable to distinguish non-viable from viable viruses
Antigen detection assay Rapid influenza diagnostic tests [#] Direct and indirect immunofluorescence assays	30 min–4 h	Detection of genotypic resistance Requires minimal technical expertise and infrastructure	Sensitivity [†] 10–70% Negative test result cannot exclude the infection Only available for some viruses
Viral isolation in cell culture	2–10 days	Higher sensitivity than antigen assays Detects viable viruses Allows virus subtyping, recovers novel and divergent strains and the detection of phenotypic resistance to antivirals Useful when specimens for virus detection were not obtained or were collected too late Recommended only for surveillance or research purposes	Less sensitive than PCR Dependent on specimen quality and transport Results not immediately available for patient care Some viruses grow poorly or not at all Lacks sensitivity in immunocompromised patients Require paired serum specimens Retrospective diagnosis
Serological tests	>14 days		

[#]: Rapid influenza diagnostic tests are faster (10–30 min); [†]: these tests have higher sensitivity for RSV than for adenovirus and influenza virus.

for subsequent characterisation. In addition and in contrast to the nucleic acid amplification test, it only detects viable viruses, which can be very useful in patient management [6].

Antigen detection assays

Direct and indirect immunofluorescence assays use commercial, type-specific monoclonal antibodies to detect viral antigens directly from clinical specimens or from cell cultures to confirm viral cytopathic effect. Mostly, these tests have a specificity greater than 80% and a variable sensitivity of between 47% and 93% depending on the type of virus and the viral load [98, 99]. Additional limitations to these tests include the lack of reagents for some viruses (human bocavirus, coronavirus and rhinovirus) and, as with viral culture, lower sensitivity in detecting dual infections compared with nucleic acid amplification methods.

In recent years, rapid antigen detection assays, sometimes called point-of-care tests, have been developed. These tests give a visual result on an immunochromatographic strip within 10–30 min, and have been developed for detecting the influenza virus, adenovirus and RSV. These assays exhibit a high specificity but limited sensitivity (10–70%) compared with PCR and viral culture [100].

The sensitivity of antigen-detection assays is significantly higher in children and when specimens are collected within the first few days of illness, since viral shedding peaks within 48 h from the onset of symptoms.

Given the limited sensitivity of these assays, a negative result does not rule out the infection and follow-up testing with PCR and/or viral culture should be considered to confirm negative test results. However, a positive result is useful due to the high specificity of these tests.

Nucleic acid amplification tests

Nucleic acid amplification is considered the most sensitive, specific and versatile test for the diagnosis of respiratory viruses and is replacing viral isolation as the reference standard. Use of PCR has augmented detection of viruses that are difficult to identify with conventional methods. As a result, overall prevalence of respiratory viral infection in PCR studies is higher than for studies in which PCR was not used. Also, the turnaround time of new techniques is 1–5 h [101].

In the literature, there is a lot of information about commercial tests and in-house assays using a variety of amplification methods [6]. RT-PCR assays combine the amplification and detection steps, shortening the assay time and reducing cross contamination. Moreover, RT-PCR can quantify the viral load in clinical specimens to assess prognosis and measure antiviral efficacy [102].

Newer multiplex PCR techniques can simultaneously detect influenza and other respiratory viruses [103].

Immunocompromised patients usually exhibit prolonged viral shedding, even despite active antiviral therapy. In cases of infection with the influenza virus this fact may contribute to an increase risk of resistant variant emergence. Any patient showing treatment failure after 3–5 days of antiviral therapy, despite ongoing therapy, should be suspected of a resistant virus infection. Sanger sequencing and pyrosequencing have been successfully used to study resistance, to the neuraminidase inhibitors and to M2 protein inhibitors [104].

Moreover, CMV, HSV and VZV can be detected by PCR in the BAL taken from HIV patients with severe respiratory infection [105].

Alternatively, bacterial pneumonia is a known complication of influenza in immunosuppressed patients. It should also be considered that virus detection does not exclude bacterial co-infection and the potential need for antibiotics [106].

Conclusion

With the diffusion of novel diagnostic tests it has been shown that viral infections in the respiratory tract are more prevalent than has previously been described. In particular viral infections are a serious clinical event in immunocompromised patients, where respiratory viruses are more frequent and aggressive than in the general population. Indeed, HIV infection is a main risk factor for increased susceptibility to viral infection and for severe clinical presentation and worse outcomes despite the notable advances of ART.

Unfortunately, a specific therapy is only available for some viral infections and it is mandatory in cases of severe disease (pneumonia) and/or immunosuppressed patients (low CD4 cell count, *etc.*). Similarly, preventive strategies are still limited nowadays and will deserve more investigation in the future. Respiratory viruses are often described in association with a bacterial pathogen (co-infection), a condition that can present worse clinical outcomes. A wide microbiological analysis is recommended in immunocompromised patients in order to optimise antimicrobial therapy.

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Other fungal and protozoan infections

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Fungal or protozoan infections of the respiratory tract are less common than viral or bacterial infectious diseases. In the immunocompetent host, most of these infections are rare and predominantly present as mild and self-limiting. Immunocompromised patients, particularly those with T-cellular immunodeficiency or prolonged neutropenia, are at increased risk of opportunistic fungal and protozoan infections and a more severe and prolonged course of disease.

Whereas candidiasis, cryptococcosis and aspergillosis are prevalent worldwide, other fungal diseases, such as histoplasmosis, coccidioidomycosis, penicilliosis and blastomycosis, are endemic to certain areas, though may also be recognised as imported diseases in nonendemic regions. Although specific and sensitive modern microbiological diagnostic tools and therapeutic options have been established for most diseases, some are either rarely available in low-income/high-prevalence countries or are not often used outside the endemic areas. Hence it is recommended that advice is sought from specialised laboratories and physicians of infectious diseases.

Most fungal infections affect both immunocompetent and immunodeficient individuals alike. While infections in otherwise healthy persons often remain asymptomatic or cause a self-limiting disease with few symptoms, immunocompromised hosts are highly susceptible to infection and symptomatic or disseminated diseases are common. Predominantly, profound T-cellular immunodeficiencies and prolonged neutropenia represent an increased risk for opportunistic fungal and protozoan infections. Hence, conditions associated with immunodeficiency are malignancies due to chemotherapy, iatrogenic immunosuppression after organ transplantation, long-term therapy with corticosteroids and advanced HIV infection. The rising number of immunocompromised individuals has increased the clinical significance of fungal infections. CD4⁺ cells are critical for antifungal defence and a decline of CD4⁺ cell numbers or impaired CD4⁺ cell function is a risk factor for invasive fungal infection. Therefore, fungal infections play an important role in AIDS-related morbidity and mortality ([table 1](#)).

Since the discovery of AIDS, opportunistic fungal infections have been recognised as major complications in HIV-infected individuals, accounting for the majority of AIDS-related deaths in early case series. With the introduction of ART into clinical practice, the prevalence of fungal infections declined but still substantially contributes to AIDS-related morbidity and mortality, with an estimated incidence of 1.5 million cases and a mortality rate of 1 million deaths per year worldwide [2].

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Table 1. Pulmonary fungal and protozoan disease with respect to the US Centers for Disease Control and Prevention (CDC) classification

Pulmonary disease	Pathogen [#]	AIDS defining (CDC-C)	HIV associated (CDC-B)
PCP	<i>Pneumocystis jiroveci</i>	Yes	
Cryptococcosis	<i>Cryptococcus neoformans</i>	No (AIDS definition is restricted to disseminated or extrapulmonary disease)	
Histoplasmosis	<i>Histoplasma capsulatum</i>	No (AIDS definition is restricted to disseminated or extrapulmonary disease)	
Coccidioidomycosis	<i>Cryptococcus immitis</i>		
Blastomycosis	<i>Blastomyces dermatitidis</i>		
Aspergillosis	<i>Aspergillus fumigatus</i>		
Penicilliosis	<i>Penicillium marneffe</i>		
Candidiasis	<i>Candida albicans</i>	Yes (AIDS defining, if pulmonary disease)	Yes (if mucocutaneous disease except oesophagus, trachea, bronchi and lung)
Ascariasis	<i>Ascaris lumbricoides</i>		
Toxoplasmosis	<i>Toxoplasma gondii</i>	No (AIDS definition restricted to cerebral toxoplasmosis)	
Cryptosporidiosis	<i>Cryptosporidium parvum</i>	No (AIDS definition restricted to chronic intestinal disease)	
Microsporidiosis	<i>Enterocytozoon bieneusi</i> <i>Encephalitozoon hellem</i>		

[#]: typical pathogen (nonexhaustive enumeration). Information from [1].

The most prevalent fungal infections in HIV infection are candidiasis, PCP and cryptococcosis. In contrast, histoplasmosis, blastomycosis and coccidioidomycosis are endemic in distinct areas of the world but are encountered only sporadically in Europe, mostly in travellers or immigrants.

The impact of aspergillosis in HIV infection has decreased since ART has been available [3, 4]. Fungal infections may occur by inhalation of spores, and for this reason, respiratory symptoms are frequently the initial manifestation of a fungal infection. However, the course of fungal disease is dependent on the immune status of the host, and dissemination to other organs or sepsis syndromes occur in patients with advanced immunodeficiency.

Similarly, patients with HIV-associated immunodeficiency are more susceptible to protozoan infections and the course of the protozoan infection is more likely to be severe. The most prevalent protozoan diseases, malaria and trypanosomiasis, do not primarily affect the lungs and are rarely described in Europe. As this chapter focuses on pulmonary manifestations, protozoan infections of the lung are briefly summarised at the end of this chapter.

Pneumocystis pneumonia

PCP was recognised in the first decade of the AIDS pandemic as a major complication and accounted for up to 70% of AIDS-related deaths in that pre-ART era [5]. Although in terms of global incidence and mortality, cryptococcoses have far outnumbered PCP cases, the latter

remains an important factor for HIV-related morbidity and mortality, and the most common AIDS-defining disease in resource-rich countries. Due to its clinical relevance, PCP will be discussed in another chapter of this *Monograph*.

Other fungal infections

Cryptococcosis

Infection with the basidiomycete *Cryptococcus neoformans* is the most common fungal infection in HIV-positive individuals worldwide. In a recent study, the global annual incidence of cryptococcosis was estimated to be 950 000 cases, with the majority occurring in sub-Saharan Africa, resulting in more than 600 000 deaths [6].

The extrapulmonary manifestation of cryptococcosis is an exclusively AIDS-defining event in the US Centers for Disease Control and Prevention classification.

Cryptococcosis is seen worldwide and, although the pulmonary disease may occur in immunocompetent hosts, the majority of patients are immunocompromised. Before the era of AIDS, only sporadic cases of cryptococcosis had been reported in western countries. Accompanying the AIDS epidemic, cryptococcosis had become more frequent, but since the introduction of ART, the incidence has declined. Nevertheless, cryptococcosis remains a common opportunistic infection in HIV-positive individuals, especially in undiagnosed or noncompliant patients and in regions where ART is not generally available [7].

Microbiology

Cryptococcosis is caused by the encapsulated yeasts *C. neoformans* and *Cryptococcus gattii*. *C. neoformans* can be divided into two serotypes according to capsular agglutination reactions. *C. gattii* is less common, and endemic to tropical and subtropical regions. *C. neoformans* has been isolated from soil samples around the world, and soil contaminated with chicken, pigeon and turkey excreta promotes its growth. Its major virulence factors are: the formation of a capsule that enables it to adhere to mucosal surfaces and prevents phagocytosis by mononuclear cells; and melatonin production that protects cryptococci from damage by oxidants. Two variants of *C. neoformans* exist, *C. neoformans* var. *neoformans* and *C. neoformans* var. *grubii*.

Asexual and sexual forms of cryptococci exist. Cryptococcal infection follows the inhalation of basidiospores or yeast cells that may cause limited pneumonitis or remain asymptomatic. Infection with *C. neoformans* often occurs in childhood and symptomatic cryptococcosis may be reactivation of a latent infection [8].

Clinical manifestations

The clinical course of cryptococcosis is largely dependent on patients' immunocompetence. In fact, contact with *C. neoformans* is common and most infections remain asymptomatic in immunocompetent hosts, although pulmonary cryptococcosis has also been sporadically reported in immunocompetent individuals [9, 10]; in contrast, it is well known that AIDS [11] or HIV infection with a CD4⁺ cell count <100 cells·μL⁻¹ is a predictor of disseminated infection [12]. Contact with *C. neoformans* is common and most infections in immunocompetent hosts remain asymptomatic; nevertheless, pulmonary cryptococcosis has been reported in immunocompetent individuals [9]. Pulmonary cryptococcosis usually manifests

with fever, cough, malaise, dyspnoea and chest pain. Radiographic findings in pulmonary cryptococcosis include: noncalcified nodules, predominantly in the basal areas of the lungs; pulmonary infiltrates; hilar lymphadenopathy; and pleural effusions [13].

In immunocompromised hosts, pulmonary cryptococcosis commonly results in haematogenous spread to other organs. Involvement of the pleural cavity and skin, with lesions resembling molluscum contagiosum, has been reported [14–16]. The most common clinical manifestation of cryptococcosis is cryptococcal meningoencephalitis, which presents with fever, headache and progressive confusion. Vision and hearing loss have been reported, and cranial nerves may be affected. Increased intracranial pressure is common [17].

Diagnosis

The diagnosis of pulmonary cryptococcosis is based on culture, histology and the detection of cryptococcal serum antigen. In cases with suspected cryptococcal meningoencephalitis, the diagnosis should be confirmed by lumbar puncture. If elevated intracranial pressure is suspected, neuroimaging should be performed prior to lumbar puncture to avoid complications and to detect intracerebral mass lesions. Cerebrospinal fluid (CSF) analysis reveals normal findings in approximately one-third of patients with cryptococcal meningoencephalitis; typical features are elevated protein and low glucose concentration. By staining of CSF samples with India ink, yeast can be identified in about 75% of cases [18].

Cryptococcal antigen

Testing for cryptococcal antigen is based on sandwich ELISA, latex agglutination or a lateral flow assay. Antigen tests can be performed using CSF; in patients with HIV, the specificity of antigen detection in serum is similar to that in CSF.

Treatment

The aim of treatment is the reduction of symptoms and the prevention of spread to the central nervous system (CNS) with severe manifestations. Therefore, therapy for cryptococcosis is recommended in all patients, even the immunocompetent, regardless of clinical symptoms.

Asymptomatic cryptococcosis in immunocompetent hosts can be treated with oral fluconazole (200–400 mg per day) or itraconazole (200–400 mg per day) for 3–6 months. In patients with mild-to-moderate symptoms, the duration of therapy should be extended to 6–12 months.

CNS cryptococcosis usually requires combination therapy with liposomal amphotericin B ($3.0\text{--}5.0\text{ mg}\cdot\text{kg}^{-1}$ per day) or amphotericin B deoxycholate ($0.4\text{--}0.7\text{ mg}\cdot\text{kg}^{-1}$ per day) and flucytosine ($100\text{ mg}\cdot\text{kg}^{-1}$ per day) for 2 weeks followed by fluconazole (400 mg) for at least 10 weeks in immunocompetent hosts. CNS cryptococcosis in HIV-positive individuals should be treated with liposomal amphotericin B ($3.0\text{--}5.0\text{ mg}\cdot\text{kg}^{-1}$ per day) or with a higher dose of amphotericin B ($0.7\text{--}1.0\text{ mg}\cdot\text{kg}^{-1}$ per day) and flucytosine ($100\text{ mg}\cdot\text{kg}^{-1}$ per day) for 2 weeks, followed by fluconazole (400 mg) [19, 20]. The toxicity of flucytosine is considerable, and a combination of amphotericin B and fluconazole (800 mg per day) has been shown to be a valid alternative [21]. Liposomal amphotericin B was less toxic and associated with higher response rates in recent studies [22]. Maintenance therapy can be discontinued if a stable CD4^+ cell count (above $200\text{ cells}\cdot\mu\text{L}^{-1}$ for at least 6 months) is achieved [23].

Histoplasmosis

Histoplasmosis was first described in 1905 in a patient from Martinique, who died after 2 months of an unexplained febrile illness [24]. Two distinct clinical entities can be distinguished that are caused by different varieties of *Histoplasma capsulatum*. Classical histoplasmosis is caused by *H. capsulatum* var. *capsulatum*, is common in North and Central America, but occurs in most tropical and subtropical areas of the world. This form is usually referred to as histoplasmosis. African histoplasmosis is caused by *Histoplasma duboisii*, which is restricted to Africa.

Most *Histoplasma* infections in HIV-positive patients occur in those with advanced disease and a CD4⁺ cell count <100 cells·μL⁻¹. Extrapulmonary or disseminated histoplasmosis has been recognised as AIDS-defining disease [25].

Microbiology

H. capsulatum is a thermally dimorphic fungus of the Onygenaceae family that exists as a mould in the environment and under culture conditions at temperatures below 35°C, and as a yeast at body temperature and in cultures above 35°C. *H. capsulatum* can be found in warm, moist soil that is rich in the excreta of bats or birds. Infection occurs by inhalation of microconidia from the soil [26].

Histoplasmosis (*H. capsulatum* var. *capsulatum*) is prevalent in temperate, subtropical and tropical areas worldwide. Endemic areas include the Mississippi, Ohio and St Lawrence River valleys of the USA, as well as parts of Central and South America, Africa, India, and the Far East. Few indigenous cases have been reported in Europe, mostly in Italy [27].

Clinical manifestations

The clinical picture of histoplasmosis is dependent on the immune function of the host and the number of inoculated spores. In immunocompetent hosts, histoplasmosis is usually asymptomatic or causes few, nonspecific symptoms, such as fever, malaise, arthralgia or nonproductive cough, that are mostly self-limited. Treatment, if necessary, is usually symptomatic [28]. Other, more severe clinical manifestations of this infection are described in the following sections.

Acute pulmonary histoplasmosis

In immunocompromised individuals or after massive inoculation of *Histoplasma*, acute pulmonary histoplasmosis usually involves several lobes of the lung, and presents as an acute severe illness with fever, chills, cough and dyspnoea. On clinical examination, rales may be heard and chest radiographs show diffuse pulmonary infiltrates.

Chronic cavitary histoplasmosis

Chronic cavitary histoplasmosis is a condition that is usually described in older patients with chronic lung diseases. Fibrosis and necrosis of pre-existing bullae results in formation of large cavities, predominantly in the upper lobes.

Granulomatous mediastinitis

Granulomatous mediastinitis is characterised by enlargement of mediastinal lymph nodes with caseous necrosis, which often melt together. Many patients remain asymptomatic; nevertheless, symptoms due to compression of mediastinal structures, such as the vena cava, bronchi or the oesophagus, can occur.

Mediastinal fibrosis

Mediastinal fibrosis is a rare but severe complication of histoplasmosis that often results in fatal outcomes and, unfortunately, usually affects younger patients. Excessive fibrosis and calcification of the upper mediastinum leads to compression of mediastinal structures.

Broncholithiasis

Calcified granulomas or lymph nodes can invade the bronchial system years after exposition, and lead to coughing and expectoration of small particles, and even to haemoptysis [29].

Disseminated histoplasmosis

Patients with defects in cell-mediated immunity are at risk of developing disseminated forms of histoplasmosis, with spread of *Histoplasma* to the bone marrow, lymph nodes, liver and spleen [30–32]. In general, spreading to any organ is possible (e.g. to the gastrointestinal tract, heart valves, bones or joints, and the CNS).

Diagnosis

Microscopy and culture

Direct microscopy and culture of specimens might provide hints for invasive fungal infection, but the tissue forms of different fungi look similar on microscopy and species identification is difficult. For the definitive diagnosis of *H. capsulatum*, genotyping should be performed.

Antigen detection and antibody tests

A sandwich ELISA is available for the detection of *H. capsulatum* antigen. The ELISA has been reported to have a greater sensitivity in urine than in sera: in patients with AIDS, a sensitivity of 95% has been reported for urine *versus* 86% in sera [33]. Several tests are available to detect antibodies against different antigens of *Histoplasma*.

Polymerase chain reaction

Identification of *H. capsulatum* DNA in specimens by PCR is possible [34].

Skin test

The histoplasmin skin test is no longer used due to several limitations. It was insensitive in acutely ill patients with disseminated infection and cross-reactive with other fungal infections, especially blastomycosis. Furthermore, the skin test could show exposure to *H. capsulatum* but was unable to discriminate active infection from premature exposure.

Treatment

In most cases of acute histoplasmosis, treatment is not necessary, but severe acute pulmonary histoplasmosis and chronic forms require antifungal therapy. In patients with acute histoplasmosis, only cases with prolonged symptoms of more than 4 weeks should be treated with itraconazole (200 mg initially, three times daily, followed by 200 mg once daily for 6–12 weeks).

In severe acute pulmonary histoplasmosis, initial therapy is with the lipid formulation of amphotericin B (3.0–5.0 mg·kg⁻¹); alternatively, the deoxycholate formulation (0.7–1.0 mg·kg⁻¹ intravenously for 1–2 weeks) is recommended. After improvement of symptoms, therapy may be continued with itraconazole (200 mg three times per day). After 3 days, the dose can be reduced to 200 mg once daily up to a total duration of therapy of 12 weeks. In patients with respiratory complications such as hypoxaemia or severe respiratory distress,

intravenous methylprednisolone ($0.5\text{--}1.0\text{ mg}\cdot\text{kg}^{-1}$) should be administered intravenously for the first 1–2 weeks [35].

Patients with chronic cavitary histoplasmosis independent of an HIV-associated immunodeficiency should receive treatment to prevent progression of the underlying pulmonary disease [36]. Itraconazole is the therapy of choice and 200 mg should be given three times per day for 3 days. Then, reduction to 200 mg is possible, for a total duration of therapy of 12 weeks (18–24 months in severe cases).

Mediastinal granulomas only require treatment if they are symptomatic. In this case, benefit from antifungal therapy has been reported [37]. Itraconazole (200 mg for 3 days), then once or twice daily for 6–12 weeks is recommended [35].

In late-stage disease like mediastinal fibrosis and broncholithiasis, antifungal therapy has no benefit. Placement of an intravenous stent can prevent obstruction of pulmonary vessels in patients with mediastinal fibrosis, and bronchoscopic removal of broncholiths is a therapeutic option in selected patients [38, 39].

Complications of histoplasmosis like pericarditis and rheumatological syndromes (e.g. arthritis and/or erythema nodosum) can be treated with nonsteroidal anti-inflammatory therapy in mild disease and with prednisone ($0.5\text{--}1\text{ mg}\cdot\text{kg}^{-1}$ daily) in severe cases. Under corticosteroid treatment, itraconazole (200 mg three times per day for 3 days and then one to two times per day for 6–12 weeks) should be given to avoid progression of the underlying disease.

In progressive disseminated histoplasmoses, the recommended initial therapy is the lipid formulation of amphotericin B ($3.0\text{--}5.0\text{ mg}\cdot\text{kg}^{-1}$) or the deoxycholate formulation ($0.7\text{--}1.0\text{ mg}\cdot\text{kg}^{-1}$) intravenously for 1–2 weeks. After improvement of symptoms, therapy may be continued with itraconazole (200 mg three times per day). After 3 days, the dose can be reduced to 200 mg for a total duration of therapy of 12 months. In milder cases, itraconazole (200 mg three times per day for 3 days and then twice daily for 12 months) is appropriate [35].

In immunosuppressed patients, lifelong maintenance therapy with itraconazole (200 mg per day) is necessary if immunosuppression is permanent; in HIV patients, discontinuation of therapy is possible if the CD4^+ cell count is stable above $150\text{ cells}\cdot\mu\text{L}^{-1}$ [40].

Coccidioidomycosis

Coccidioidomycosis is a fungal infection caused by the thermally dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*; it was first described in 1892 [41]. *Coccidioides* spp. are endemic to parts of the American continent. Inhaled arthroconidia, the fungal spores of *Coccidioides* spp., are able to escape the mucociliary clearance of the upper respiratory tract. Inside the host or in culture, the arthroconidia transform into spherules, structures containing endospores that are released after rupture of the spherule [42, 43].

An increase of the incidence of coccidioidomycosis has been reported in endemic areas, which is partly due to a rising number of cases in patients with HIV infection or other immunodeficiencies [44]. In the early HIV epidemic, coccidioidomycosis was associated with extremely high mortality [45]. Extrapulmonary and disseminated forms of coccidioidomycosis are AIDS-defining diseases.

Clinical manifestations

In immunocompetent hosts, 60% of coccidioidomycoses remain asymptomatic or have few symptoms. If symptoms occur, they are usually self-limited and resemble CAP. The onset of ambiguous symptoms is usually 2–3 weeks after exposure, with fever, cough, chest pain, fatigue and arthralgias. Skin manifestations such as a rash or erythema nodosum occur in 10% of cases. Chest radiographs may show infiltrates, pleural effusions or hilar lymphadenopathy. In nearly all immunocompetent cases, symptoms subside without specific treatment. Few patients develop chronic, progressive or disseminated disease [46].

In HIV patients who are not severely immunocompromised, the clinical manifestations are similar to those of HIV-negative individuals with few symptomatic infections. Risk factors associated with symptomatic infection in HIV patients are a CD4⁺ cell count <250 cells·μL⁻¹ and a previous diagnosis of AIDS [47].

In progressed HIV infection, coccidioidomycosis often presents with bilateral pulmonary infiltrates displaying interstitial abnormalities and nodules on chest radiographs that can be misinterpreted as PCP. The mortality in patients with diffuse pulmonary infection is high and has been shown to be up to 80% [48].

Disseminated coccidioidomycosis, defined as spread of the disease beyond the thoracic cavity, is more common in HIV-positive individuals. Meningitis, lymph node and skin manifestations have been described in HIV patients, whereas bone and joint involvement is rare [45, 48].

Diagnosis

The diagnosis is based on serological tests, histopathology and culture; however, serological tests in HIV-positive individuals are less reliable than in the immunocompetent. The timing of serologic testing may be critical for interpretation of the results as the early IgM antibody becomes measurable between 1–3 weeks after onset and IgG antibodies in the second or third week. IgG antibodies remain for months and correlate with the activity of the disease [42].

Treatment

In most cases of coccidioidomycosis in HIV-negative patients, specific treatment is not necessary as the infection is self-limited.

The guidelines of the Infectious Diseases Society of America recommend treatment of symptomatic coccidioidomycosis in HIV-positive individuals with a CD4⁺ cell count <250 cells·μL⁻¹, and some experts recommend treatment of all HIV-positive individuals with symptomatic coccidioidomycosis regardless of the CD4⁺ cell count [49].

As observational studies have shown, predominantly fluconazole (400 mg per day), itraconazole (200 mg twice daily) or ketoconazole (400 mg per day) have been used. Treatment was necessary up to several months and relapses may occur after cessation of therapy. Therefore, even patients with less severe illness or without evidence of immunodeficiency should be carefully followed for a year or longer [49, 50]. Treatment options include amphotericin B (deoxycholate and lipid formulations) and azole derivatives. Diffuse pneumonia should be treated with amphotericin B or high doses of fluconazole. Initiation therapy with amphotericin B can be discontinued after improvement of symptoms and followed by an oral azole. The total treatment duration should be not less than 12 months. In severe cases of disseminated disease, a combination of amphotericin B and an

azole derivate has been suggested to be more effective than monotherapy. Maintenance therapy should be continued in HIV-infected persons until $CD4^+$ cells reach $250 \text{ cells} \cdot \mu\text{L}^{-1}$. Patients with meningitis may require lifelong therapy [49].

Blastomycosis

Blastomycosis is a fungal infection caused by *Blastomyces dermatitidis*, the asexual form of *Ajellomyces dermatitidis*. Endemic areas include America, Africa and India.

Infection occurs by inhalation of conidia from contaminated soil [51, 52].

Clinical manifestations

As with other dimorphic fungi, blastomycosis may be asymptomatic or cause a mild, often self-limiting respiratory disease in immunocompetent hosts. Nevertheless, even in the absence of cellular immunodeficiency, diffuse pulmonary and disseminated infection with involvement of skin, bones, the genitourinary tract or the CNS occurs more commonly than in histoplasmosis.

Immunocompromised individuals are at high risk of diffuse pulmonary and disseminated infection, which are associated with high mortality. The clinical features of blastomycosis are indistinguishable from other fungal infections, TB or neoplastic diseases [51–53].

Diagnosis

The diagnosis is made on the basis of serologic tests, DNA typing, histopathology and culture. The diagnosis of blastomycosis can be difficult to establish and is mainly dependent on culture and direct microscopy. Neither skin nor serologic testing has been shown to be reliable, and in serologic diagnostics, optimal timing of testing has to be considered. Antigen tests might be helpful in establishing the diagnosis [54].

Treatment

Spontaneous resolution has been reported in immunocompetent patients with acute pulmonary blastomycosis. Antifungal treatment is recommended in all patients with acute or chronic pulmonary disease and especially in patients with extrapulmonary manifestations. Therapeutic options include amphotericin B and azole derivatives [55]. In patients with mild-to-moderate symptoms of pulmonary or extrapulmonary blastomycosis, itraconazole (200–400 mg per day) is appropriate. In patients with life-threatening or disseminated infections, or CNS manifestation, as well as in immunocompromised patients, therapy with amphotericin B ($0.7\text{--}1.0 \text{ mg} \cdot \text{kg}^{-1}$ per day with a maximum dose of 1.5–2.5 g) should be initiated. After clinical improvement, switching to oral fluconazole is possible [55].

Aspergillosis

Pulmonary aspergillosis is a rare but severe complication of advanced HIV infection. Patients with $CD4^+$ cell counts $<50 \text{ cells} \cdot \mu\text{L}^{-1}$ or those on long-term corticosteroid therapy are at highest risk, while fortunately, in areas where ART is widely available, the disease has become rare [56].

Aspergillus is a ubiquitous mould that has been isolated from soil, dust and air. Of the 35 *Aspergillus* species that cause diseases in humans, *Aspergillus fumigatus* is the most common, accounting for 95% of human infections. Aspergillosis is caused by inhalation of conidia that

germinate in the airways; hyphae then invade the lung parenchyma. Dissemination occurs after invasion of vascular structures.

Clinical manifestations

The most common symptoms of pulmonary aspergillosis are cough, fever, malaise, dyspnoea and thoracic pain. Extrapulmonary manifestations typically affect the CNS but manifestations in the sinuses, heart, liver and kidneys have also been reported [56–58]. Conventional chest radiography remains normal in the initial course of disease and infiltrates or cavitary lesions are rarely visible. For the diagnosis of pulmonary aspergillosis, high-resolution computed tomography is more sensitive than conventional chest radiography [59].

Patients with invasive aspergillosis generally appear severely ill. Dissemination of fungi can lead to sepsis syndrome with multiorgan failure [60].

Diagnosis

Antigen testing for galactomannan or β -D-glucan is available and a positive result can hint at aspergillosis. However, the tests have only been evaluated in patients with haematological malignancies and not in HIV-positive individuals [61]. The diagnosis is made on the basis of histopathology and culture. In some cases, differentiation between invasive infection and colonisation can be difficult.

Treatment

Therapeutic options include azole derivatives, especially voriconazole and posaconazole; polyenes (amphotericin B); and echinocandins.

In invasive pulmonary aspergillosis, voriconazole ($6 \text{ mg} \cdot \text{kg}^{-1}$ intravenously every 12 h followed by $4 \text{ mg} \cdot \text{kg}^{-1}$ every 12 h for a minimum of 6–12 weeks in immunosuppressed patients until the lesions have resolved) is the recommended therapy. Alternatively, liposomal amphotericin B, caspofungin, micafungin or posaconazole can be given. Under some conditions, like severe sepsis in neutropenic patients, primary combination therapy can be considered [62].

Penicilliosis

Penicillium marneffei is the only species of the genus *Penicillium* that is a dimorphic fungus. It is endemic to South-eastern Asia. In endemic areas, *P. marneffei* is a major cause of AIDS-related morbidity and mortality [63].

Although the exact route of infection is not entirely clear, inhalation of conidia is the suspected route of transmission, as for other dimorphic fungi.

Clinical manifestations

Asymptomatic infections have been reported in persons from endemic countries and the course of the disease is dependent on immune function, with most cases occurring in patients with advanced HIV infection and CD4^+ cell counts $<100 \text{ cells} \cdot \mu\text{L}^{-1}$.

The clinical picture is similar to histoplasmosis and other fungal infections involving the respiratory system, with fever, cough, dyspnoea and chest pain. Haematogenous spreading leads to affection of the skin, joints or bones. Manifestation in the gastrointestinal tract with diarrhoea is common and present in 30% of cases [64–76].

Diagnosis

The diagnosis is established on the basis of culture and histopathology.

Treatment

In milder cases in immunocompetent patients, oral treatment with itraconazole (200 mg twice daily for 8–12 weeks) seems to be appropriate [67]; severely ill patients and immunocompromised individuals should receive therapy with amphotericin B (0.6 mg·kg⁻¹ per day intravenously for 2 weeks) followed by itraconazole (200 mg twice daily for 10 weeks). In HIV-positive individuals, maintenance therapy can be discontinued if CD4⁺ cell counts are >100 cells·μL⁻¹ [68].

Candidiasis

Infection with *Candida* spp. is common in advanced HIV infection, manifesting as oropharyngeal candidiasis and oesophagitis. In females, candidal vulvovaginitis is another important manifestation. Candidiasis of the oesophagus, trachea, bronchi and lungs are AIDS-defining diseases. *Candida* pneumonia is extremely rare. Mucocutaneous candidiasis correlates with reduced CD4⁺ cell counts and the prevalence increases significantly in patients with CD4⁺ cells <200 cells·μL⁻¹. In a recent study, the prevalence of mucocutaneous candidiasis in newly diagnosed HIV patients in the USA was 27% [69].

Candidaemia and invasive candidiasis primarily occur in immunodeficient persons, especially those with impaired T-cell function. Predisposing factors for invasive candidiasis are patients with haematological malignancies receiving chemotherapy, solid-organ transplant recipients and patients in intensive care units. Invasive candidiasis can affect the urinary tract, bones, joints, meninges, heart valves or eyes as a consequence of haematogenous spread. Candidaemia, the presence of *Candida* in the blood, is often driven by plastic catheters or implants, and can lead to a febrile fever disease and even result in a sepsis syndrome with multiorgan failure.

A severe complication of candidemia is endogenous candida endophthalmitis, a hematogenous seeding of fungi into the eye. Endogenous candida endophthalmitis usually first affects the choroid, due to the high vascularisation presenting as chorioiditis or chorioretinitis. If the infection progresses into the vitreous humour, vitritis or even involvement of the aqueous humour may occur [77].

Diagnosis

The diagnosis of mucocutaneous candidiasis is made clinically in cases with suspected invasive disease culture and antigen tests are available.

Treatment

Treatment of mucocutaneous candidiasis involves azoles or nystatin in limited disease. In HIV-associated oropharyngeal candidiasis, systemic therapy has been shown to be more effective than topical treatment [70].

Candidaemia and invasive candidiasis should be treated according to the immune status of the patient and their neutrophil count, using azole derivatives, amphotericin B or an echinocandin [71].

Candidaemia and invasive candidiasis should be treated according to the immune status of the patient and their neutrophil count. In the absence of neutropenia, fluconazole (loading dose of 800 mg (12 mg·kg⁻¹), then 400 mg (6 mg·kg⁻¹) daily) or an echinocandin

(caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) is recommended for at least 14 days. In neutropenic patients, LFAmB (3–5 mg·kg⁻¹ daily), caspofungin (loading dose of 70 mg, then 50 mg daily) or voriconazole (6 mg·kg⁻¹ administered intravenously twice daily for two doses, then 3 mg·kg⁻¹ twice daily) are recommended therapies. Therapy should continue for at least 14 days after clearance of fungi from the blood stream has been documented [70].

In cases of endogenous candida endophthalmitis, vitrectomy, intravitreal injection of amphotericin (5–10 µg in 0.1 mL sterile water) or voriconazol (5–10 µg in 0.1 mL sterile water) and systemic therapy are recommended [77].

Protozoan infections

As in fungal diseases, patients with HIV/AIDS are more susceptible to protozoan diseases, particularly if they are severely immunocompromised. Malaria, the globally most common protozoan disease, is a burden in countries where rates of co-infection with HIV are high [72]. However, malaria is a systemic disease affecting mainly the red blood cells, liver and CNS; the respiratory system is not primarily affected.

Pulmonary toxoplasmosis

Descriptions of pulmonary toxoplasmosis were predominantly from the pre-ART era and most cases were from France [73]. In cases with advanced immunodeficiency, infection with *Toxoplasma gondii* presents as a pulmonary syndrome with fever, coughing and dyspnoea. Bilateral interstitial infiltrates are common findings in chest radiographs and hilar lymphadenopathy is usually present. Treatment is similar to that for other manifestations of toxoplasmosis, with pyrimethamine and sulfadiazine, or pyrimethamine and clindamycin [74].

Treatment is similar to that of other manifestations of toxoplasmosis: pyrimethamine (two doses of 50 mg per day (after 3 days, reduction to two doses 25 mg per day)) plus sulfadiazine (four doses of 500–1000 mg per day) and leucovorin (10–25 mg daily) or pyrimethamine (two doses of 50 mg per day (after 3 days, reduction to two doses of 25 mg per day)) plus clindamycin (four doses of 600 mg) and leucovorin (10–25 mg daily). Alternative treatment regimen include pyrimethamine (two doses of 50 mg per day (after 3 days, reduction to two doses of 25 mg per day)) plus atovaquon (two doses of 1500 mg) and leucovorin (10–25 mg per day). Maintenance therapy should be continued at half of the therapeutic dose until CD4⁺ cells are stable at >200·µL⁻¹.

Pulmonary cryptosporidiosis and microsporidiosis

Pulmonary manifestations of primary intestinal protozoan or fungal diseases are rare in infection with *Cryptosporidium parvum* and *Microsporidium* spp., both of which are common causes of diarrhoea in HIV-positive patients, even though more than 100 cases of cryptosporidiosis and microsporidiosis have been described in the literature to date.

Although as yet no established antimicrobial therapy exists for these infections, treatment of cryptosporidiosis with paromomycin and azithromycin has been reported to be successful [75, 76, 78, 79].

Data from case reports and case series in immunocompromised patients suggest that nitazoxanide (500–1000 (up to 1500) mg twice daily) should be administered. Long treatment periods of up to several years have been reported with response rates in more than a half of the patients [80]. Alternatively, combination therapy with azithromycin (500–600 mg per day) and the non-absorbable paromomycin (25–35 mg·kg⁻¹ per day) has been described in case reports [81, 82].

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Pulmonary malignancies

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Cancer is frequent in patients with AIDS. This chapter deals with three neoplastic diseases that can occur in the thorax: lung cancer, which is the most frequent in western countries; and Kaposi's sarcoma and non-Hodgkin lymphoma, which are two of three cancers that define AIDS. The epidemiology, clinical presentation, treatment and prognosis are reviewed for these three particular tumours in the context of AIDS.

Neoplastic diseases are part of the definition of the symptomatic phase (stage C) of AIDS. This stage is defined, in adults, by the occurrence of opportunistic infections like TB or PCP, manifestations related to HIV such as encephalitis, cachexia, or the development of some cancers like non-Hodgkin lymphomas, cervical carcinoma and Kaposi's sarcoma (KS). These cancers are due to oncogenic viruses: EBV, human papillomavirus (HPV) and human herpesvirus (HHV)8 (also known as KS herpesvirus). Other cancers that are not included in the AIDS definition are also more frequent in patients with AIDS than in the immunocompromised patient. These are: Hodgkin lymphoma, lung cancer, anal cancer, melanoma and skin cancers ([table 1](#)).

Cancer epidemiology in AIDS

AIDS was reported for the first time more than 30 years ago, in the early 1980s. It was then a very rapidly fatal disease. The initial clinical presentation could be an AIDS-defining cancer: non-Hodgkin lymphoma, KS or cervical carcinoma. With the development of effective treatment, particularly ART, patient survival has become much longer and other cancers may appear during the course of the disease, such as lung cancer [1]. So, it is important to separate the modern therapy era from the older periods when analysing epidemiology of neoplastic diseases in AIDS. The purpose of this chapter is to briefly summarise the current data on cancer in AIDS patients, particularly in industrialised countries (mainly Europe and North America) where patients benefit from ART.

Since 1996 and the introduction of the so-called tritherapy against AIDS, the occurrence of KS has significantly decreased after the initiation of the treatment. In the EuroSIDA study, a European prospective study including 9803 patients with HIV-1 infection [2], the incidence of KS after AIDS diagnosed between 1994 and 2003 has decreased, with an estimated annual reduction of 39%, while the percentage of initial AIDS diagnosis remains stable around a rate

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Table 1. Main cancers with an increased incidence in AIDS patients

AIDS-defining cancers	Non-AIDS-defining cancers
Non-Hodgkin lymphoma	Lung cancer
Kaposi's sarcoma	Hodgkin lymphoma
Cervical carcinoma	Anal cancer
	Leukaemia
	Brain tumours
	Melanoma

of 6%. In the USA [3], on the basis of a series of data provided by 263 254 cases, the overall incidences of KS and non-Hodgkin lymphoma (at and after AIDS diagnosis) have declined with the use of ART. The incidence per 10 000 person-years has decreased from 1282 to 190 for KS and from 1226 to 306 for non-Hodgkin lymphoma, while it remained stable but low for cervical carcinoma.

For non-AIDS-defining cancers, however, a major increase in incidence is observed. A meta-analysis [4] has shown that AIDS predisposes to various cancers. The analysis used standardised incidence ratios (SIRs) collected in 18 studies with a total of 625 716 HIV-infected patients and 4797 non-AIDS cancers. The most frequently observed non-AIDS cancer type was lung cancer (n=847), followed by Hodgkin lymphoma (n=643) and anal cancer (n=254). In comparison with the general population, AIDS was associated with greater SIRs for leukaemia (8.02), brain cancer (4.86), lung cancer (3.01), Hodgkin lymphoma (2.77) and all non-AIDS cancers combined (3.17). Except for kidney and breast cancers, the SIRs did not appear to be different for the remaining cancer sites in the ART era.

In the US series [5], after the introduction of ART, lung cancer was the most frequent cancer (incidence of 100 cases per 10 000 AIDS patients) followed by anal cancer (62 cases), Hodgkin lymphoma (41 cases) and oral cavity/pharyngeal cancers (40 cases). The incidence of non-AIDS-defining cancers has increased after the use of ART from 332 to 448. In the EuroSIDA cohort [6], an analysis of 356 non-AIDS-defining malignancies showed that a low current CD4⁺ cell count was associated with an increased incidence of some non-AIDS-defining cancers, such as anal cancer, Hodgkin lymphoma and lung cancer. In a study conducted in France [7], the number of new malignancies for the year 2006 in AIDS patients was estimated to be 1320, 68% of which were non-AIDS-defining cancers. This represents an incidence more than three times higher than in the general population. The most frequent malignancies were non-Hodgkin lymphomas followed by KSs. For non-AIDS-defining malignancies, lung cancer was the most frequent followed by anal cancer and Hodgkin lymphoma.

Therefore, cancer is an important cause of death in AIDS patients. In the EuroSIDA study [8], 1826 deaths observed in 8556 subjects were analysed. Death rate declined between 1994 and 2001 with an increased proportion of patients who died without an AIDS-defining illness. In a US registry of 83 282 patients with AIDS [5], mortality rate also decreased markedly over time with an increased proportion of deaths due to non-AIDS-defining cancers, lung cancer being the most frequent cause (22%) in the ART era. Similar figures have been reported in a French study [9], with lung cancer being the first cause of death due to non-AIDS-defining cancers.

Thus, lung cancer appears to be an important problem in AIDS patients, who are at higher risk of that neoplasia than the general population. Lymphoma and KS are also frequent.

There are no good epidemiological data about their initial occurrence in the thorax in order to compare their incidence in the lungs in comparison to lung cancer.

Lung cancer

Clinical presentation

HIV patients frequently present with radiological lung abnormalities, either on plain chest radiography or on computed tomography (CT), of which most are related to infectious aetiologies [10]. In a retrospective review [11] including 44 HIV patients with chest radiographic abnormalities but without pulmonary symptoms, nodular masses and enlarged nodes were the prominent features (57% and 17%, respectively). Mycobacterial (tuberculous or nontuberculous) infection was encountered in half of the cases and KS in 12%. Nonsmall cell lung carcinoma (NSCLC) was found in only one patient (2%). In another retrospective study, 87 out of 242 HIV patients had at least one pulmonary nodule on chest CT [12]. An opportunistic infection was documented in 57 cases and four cases of lung cancer were observed. These observations illustrate the difficulties in diagnosing lung cancer in AIDS patients with lung nodules that are more frequently due to opportunistic infections than lung cancer. In a small study, BAZOT *et al.* [13] looked at the radiological presentation of lung cancer in HIV patients. The radiological presentations were mostly parenchymal masses and nodules, while alveolar condensation was found in only one case; enlarged lymph nodes were also common.

Incidence

The first case of lung cancer in an HIV patient was published 30 years ago. The authors reported the case of a 35-year-old homosexual man presenting with an adenosquamous metastatic lung cancer [14]. Further to that, two cases were described concerning small cell lung cancer [15, 16]. Since then, an increasing number of reports has become available on a possible association of lung cancer with HIV infection. Currently, lung cancer is a non-AIDS-defining cancer. Recent reviews summarised the current evidence on the incidence of lung cancer, showing overall that lung cancer incidence is two to four times higher than expected in HIV patients. The relative risk and/or SIRs ranged from 0.8 to 14.1 [17]. An increase was observed in the ART era, which is possibly explained by better control of the HIV disease and a reduced mortality from AIDS, allowing the time to develop smoking-related diseases like lung cancer [18, 19].

The lung cancer–AIDS association

Different hypotheses have been proposed to explain the propensity of HIV patients to develop lung cancer. The main causal factor is smoking exposure, present in 85–100% of HIV lung cancer cases. Favouring this hypothesis, lung cancer never occurred in nonsmokers from a Swiss HIV cohort [20]. However, other aetiological options have been advanced based on analyses showing that HIV infection is a risk factor for lung cancer after adjustment for smoking status (hazard ratio (HR) 3.6, 95% CI 1.6–7.9) [21]. Indirect arguments showed that immunosuppression could be a risk factor. In a meta-analysis, similar SIRs for lung cancer were found in HIV (2.72, 95% CI 1.91–3.87) and transplants recipients (2.18, 95% CI 1.85–2.57) [22], while a relationship between the occurrence of lung cancer and AIDS was found in another meta-analysis, with a SIR between AIDS and non-AIDS patients of 3.01 (95% CI 1.69–5.38) [4]. The delay between HIV and lung cancer diagnoses can be important, with

means of 7–11 years, although lung cancer can be the presenting feature of HIV infection [23, 24]. However, there is no clear relationship between the CD4⁺ cell count and risk of lung cancer, with the exception of AIDS-defining cancers such as KS [18, 25], although increased CD4⁺ cell count was reported to be a favourable prognostic factor for survival in HIV patients with lung cancer [23, 24]. Viral aetiologies, including HIV, HHV8 and HPV, have been investigated but no relationship with lung cancer occurrence could be confirmed [18]. The source of HIV infection (homosexual or heterosexual contact, or drug abuse or other blood contamination) seems to be of no importance in the risk of developing lung cancer [18, 19].

Does lung cancer in HIV patients have different characteristics from that in HIV-negative people? The main differences concern smoking status, as described earlier, and age at lung cancer diagnosis. In HIV patients, the mean age at lung cancer diagnosis is around 45–50 years (and may even be under 40 years), which is at least a decade younger than the mean age of lung cancer occurrence in general population (around 65–70 years) [17–19]. Two recent retrospective cohorts showed a median age of 52–55 years [23, 24]. In addition, there is a large male predominance, although this could more reflect the sex distribution of HIV-infected patients and not really be a predisposing factor for lung cancer. Otherwise, as for HIV-negative patients, NSCLC represents the vast majority of lung cancer [17–19], with adenocarcinomas the leading cause followed by squamous cell carcinoma. Contrary to what was expected from initial reports, the stage distribution is similar or only slightly different from that of the general lung cancer population, with stages III–IV accounting for around 80% of the cases [18, 19, 26]. Some reports suggest that performance status (PS) is more frequently altered at diagnosis in HIV patients [18, 19]. In a recent German cohort, 45% of the patients had PS >1 at lung cancer occurrence [23].

While symptoms associated with lung cancer have the same distribution as in HIV-negative patients, lung cancer in AIDS is more frequently symptomatic at diagnosis [17, 18]. In a small case–control study, KARP *et al.* [27] showed as early as 1993 that respiratory complaints (cough, dyspnoea, tachypnoea and chest pain) and weight loss, but also fever and night sweats are predominant.

Treatment and prognosis

The earliest reports demonstrated a poor prognosis in HIV patients with lung cancer and limited access to active treatment [28]. Further studies consistently showed reduced survival in HIV-positive patients in comparison with HIV-negative patients (table 2), incorporating mainly, but not exclusively, advanced-stage NSCLC. These results are subject to biases, as detailed treatment information for all HIV-positive and -negative groups are not available, and no multivariate analyses were performed taking into account the major prognostic factors of lung cancer. A recent German cohort also showed a median survival time (MST) of 0.81 years for patients treated with palliative intent, while it remained adequate for stage I–IIIA patients receiving curative treatment, with a MST of 5.18 years [23]. In another cohort, MST was 6.1 months but was only 4 months for stage III–IV disease and around 2.5 years for stage I lung cancer [24]. While an increase in lung cancer incidence in the post-ART period was observed, a positive role of ART in survival has been suggested. In a French series of 49 patients, three prognostic factors for survival were found on multivariate analysis: use of ART (HR 0.4, 95% CI 0.2–0.9; $p=0.027$), PS ≤ 1 (HR 0.2, 95% CI 0.09–0.46; $p=0.0001$) and stage I–II disease (HR 0.15, 95% CI 0.04–0.53; $p=0.003$) [35]. In another series, no difference in survival was noted according to use of ART ($p=0.39$) [26]. It must be pointed out that a significant number of patients in these studies received any treatment at all, whereas active

anticancer treatment could itself be an independent prognostic factor for survival (HR 4.17, 95% CI 1.89–9.18; $p=0.0004$) [24]. However, in the ART period, the number of untreated lung cancer patients remains significant, from 12% [23, 35] to 29% [24], mainly because of alteration of their general status or because they decline proposed treatment.

There are no specific therapeutic guidelines for HIV patients with lung cancer. For early stages, surgery is the cornerstone and adequate survival rates have been obtained without excessive surgical complications [19, 24, 35]. In general, those patients have higher CD4⁺ cell counts, low viral load and good PS. While some patients received perioperative chemotherapy, the role of induction/adjuvant chemotherapy for surgical stages cannot be assessed due to a lack of data. Radiotherapy alone or in combination with chemotherapy appears feasible but should be viewed with some caution, as radiosensitising properties of some antiretroviral agents, such as nelfinavir, has been suggested in a case report [36]. There are some concerns regarding chemotherapy administration in HIV patients. First, chemotherapy adds immunosuppression to that induced by the HIV infection, increasing the risk of opportunistic infections by decreasing CD4⁺ cell counts. However, few patients die from treatment-related complications, but rather from cancer evolution [18]. The main problem is the interaction between antiretroviral drugs and chemotherapy agents, and added toxicity when combining both therapies. Drugs like etoposide, taxanes and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (gefitinib and erlotinib) are metabolised by cytochrome P450, which is inhibited by protease inhibitors. Nucleoside analogues can induce myelosuppression, and agents like ritonavir inhibit the permeability glycoprotein efflux pump involved in the elimination of vinca alkaloids and taxanes from cells. Some other antiretroviral agents (zidovudine, stavudine, *etc.*) have a peripheral neurotoxicity that could compete with cisplatin or taxanes. These interactions were summarised in an excellent review in 2010 [37]. The authors concluded that “Pharmacokinetics data and clinical cases pinpoint to potential life-threatening interactions between protease inhibitors [...] and taxanes, vinca alkaloids, as well [EGFR tyrosine kinase inhibitors] and irinotecan.” [37].

Lung cancer is becoming the most frequent cause of cancer death in HIV patients. It is frequently symptomatic at diagnosis, which possibly explains the large number of untreated patients. While there are concerns regarding added toxicity between antiretroviral drugs and anticancer treatment, AIDS patients can receive active therapy against lung cancer. The therapeutic strategy needs to be individualised, taking into account HIV history, CD4⁺ cell count and viral load, and the potential toxicity of chemotherapy, by a multidisciplinary team.

Kaposi's sarcoma

KS is a low-grade vascular tumour related to HHV8 [38]. Before the advent of ART, pulmonary KS was reported in approximately 10% of patients with AIDS, 25% of these having cutaneous KS, and in roughly 50% of *post mortem* examinations, patients had AIDS, KS and respiratory infections. Since the use of potent cART became widespread, the incidence of KS has declined precipitously in North America and Europe [39]. IRIS after starting ART has been well characterised. Paradoxical KS-IRIS occurs, on average, in 20% of patients starting ART.

Clinical presentation and diagnosis

In most cases, pulmonary KS occurs in conjunction with extensive mucocutaneous involvement. However, lung location can be the initial manifestation of KS (<15% of cases).

Patients with pulmonary KS more often present with cough, dyspnoea and fever [40], but also sometimes with haemoptysis or chest pain. In some cases, imaging abnormalities on chest radiography or CT will be the only findings suggestive of pulmonary involvement in asymptomatic patients. Findings on chest CT suggestive of pulmonary KS are: nodular or peribronchovascular opacities; thickened interlobular septa; lymphadenopathies; and pleural effusions (fig. 1).

Patients with KS typically have a low CD4⁺ cell count and a high HIV viral load, unlike classical lung cancer. The diagnosis of AIDS-related pulmonary KS is often clinical, based on the presence of mucocutaneous disease, compatible features on chest CT and, eventually, endobronchial, cherry-red or purple, slightly raised lesions characteristic of KS. Transbronchial brushings/biopsies and analysis of pleural fluid are not very helpful [41] but pulmonary KS is well documented in large tissue sections available from open-lung biopsy. Pulmonary function tests are sensitive in detecting the pulmonary abnormalities due to KS. A low diffusion capacity, lack of arterial desaturation with exercise and airflow obstruction are suggestive of this diagnosis [41].

A detailed evaluation should exclude an infectious aetiology or other tumours. Indeed, the frequency of pleuropulmonary disease in KS represents less than 15% of pneumonitis observed in HIV-infected patients. In biopsy specimens, KS is an angioproliferative tumour characterised by slit-like neovascular processes, and proliferating endothelial cells, fibroblasts, leukocytes and spindle-shaped tumour cells. Positive nuclear immunostaining for HHV8 can be found (fig. 2).

Treatment and prognosis

ART is a key component when treating patients with KS and is considered an effective anti-KS therapy in 60–70% of patients with limited cutaneous lesions [42–44]. Although ART may

Table 2. Comparison of survival rates in HIV-positive and indeterminate patients with lung cancer

First author [ref.]	Type of study	Patients n		Median survival time		Statistical significance
		HIV ⁺	Indeterminate	HIV ⁺	Indeterminate	
POWLES [29]	Prospective database	9	27	4 m	4 m	p=0.55
SRIDHAR [30]	Matched case-control	19	32	3 m	10 m	p=0.0026
	Retrospective					
TIRELLI [31]	Matched case-control	36	102	5 m	10 m	p=0.0001
	Retrospective					
VYZULA [32]	Unmatched case-control	11	49	31 w	48 w	p=0.0035
	Retrospective					
D'JAEN [26]	Unmatched case-control	75	169 091	9 m	9 m	p=0.43
	Retrospective					
BROCK [33]	Unmatched comparison with SEER registry	92	4973	6.3 m	9.4 m	HR 4.57, 95% CI 1.25–1.96
	Retrospective					
ALSHAFIE [34]	Retrospective	11	116	4 m	7 m	p=0.003

m: months; w: weeks; SEER: Surveillance, Epidemiology, and End Results; HR: hazard ratio.

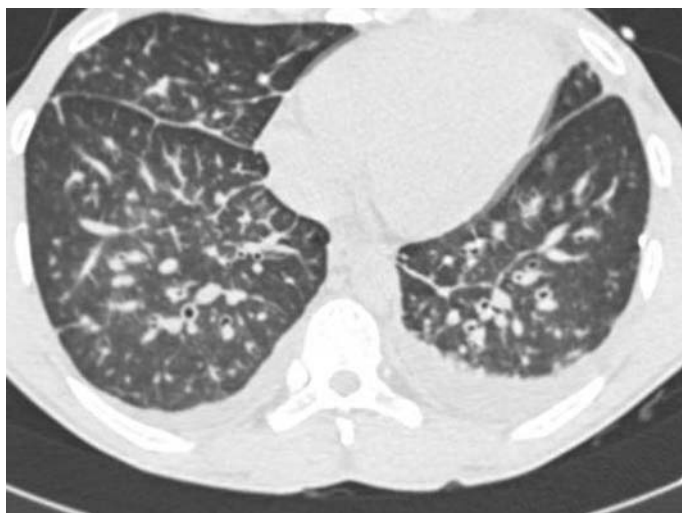


Figure 1. Pulmonary Kaposi's sarcoma features on computed tomography (CT). Nodular or peribronchovascular opacities, thickened interlobular septa and pleural effusion on chest CT are suggestive of pulmonary Kaposi's sarcoma. Image courtesy of J.C. Goffard (Cliniques Universitaires Erasme, Université Libre de Bruxelles, Brussels, Belgium).

be sufficient to induce regression of KS in some cases, the addition of systemic chemotherapy is indicated in patients with symptomatic lung KS or evidence of disease progression despite ART. Active cytotoxic agents include vinca alkaloids, anthracyclines, bleomycin and etoposide. Response rates of 30–50% are typical and responding patients may achieve dramatic improvements in pulmonary symptoms. Randomised studies have established PEGylated liposomal (L)-doxorubicin or L-daunorubicin as the first-line chemotherapy, with objective response rates ranging from 59% to 82%, and better tolerance compared with combined chemotherapy regimens [44–46]. Second-line chemotherapy relies on paclitaxel, which provides high response rates (60–70%) in patients with anthracycline-resistant disease [47],

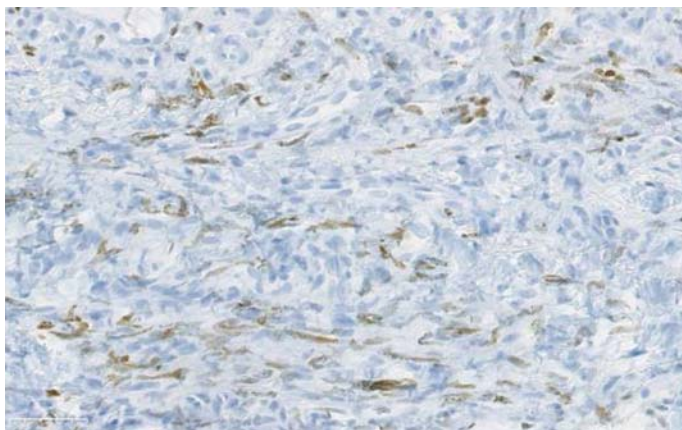


Figure 2. Human herpesvirus (HHV)8 in a pulmonary Kaposi's sarcoma. Positive nuclear immunostaining for HHV8 is shown on a biopsy specimen. Image courtesy of N. De Saint Aubain (Institut Jules Bordet, Université Libres de Bruxelles, Brussels, Belgium).

but experience in pulmonary KS is limited. Chemotherapy may improve respiratory impairment in patients with extensive pulmonary KS but the outcome remains poor (median survival between 3 and 11 months).

In patients with symptomatic endobronchial obstruction due to KS, therapy is aimed at securing the patency of the airway to achieve adequate ventilation and oxygenation. This may include endoscopic laser resection, stent placement and/or radiation therapy.

For patients with pleural KS, the use of repeated thoracentesis in combination with ART and chemotherapy can improve symptoms. If a pleural effusion recurs quickly, an indwelling pleural catheter can be placed or talc pleurodesis performed, although experience in pleural KS is limited.

Non-Hodgkin lymphoma

Despite changes in epidemiology and improvements in survival in the ART era, lymphoma remains a major cause of morbidity and mortality in HIV-infected patients [48, 49]. HIV patients usually present more aggressive histological subtypes of lymphoma and advanced-stage diseases. In this population, lymphoma is principally of B-cell origin, mostly Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL) [50]. EBV and HHV8 have been implicated in the development of HIV-associated lymphoma, such as *via* immunosuppression and chronic B-cell activation [51]. With improvements in HIV therapeutics, a majority of the patients will be able to tolerate the standard recommended therapy. However, because of increased toxicity, particular attention should be paid to supportive care. IRIS after starting ART can occur, as for KS, unmasking lymphoma-IRIS in 12% of patients.

Clinical presentation and diagnosis

In addition to classical assessment, for staging, the initial evaluation should include the following information. 1) Parameters of HIV infection: CD4⁺ cell count and HIV viral load. 2) Co-infection with other viruses (HBV and HCV); brain and cerebral spinal fluid investigation in DLBCL and Burkitt lymphoma. 3) Comorbidity assessment: cardiovascular, pulmonary, neurological and renal evaluation. 4) Previous history of opportunistic infections.

Pulmonary manifestations of lymphoma may result from extranodal involvement, contiguous infiltration from lymph nodes, primary pulmonary lymphoma, enlargement of the lymph nodes and pleural effusion.

Lymphoma in HIV-infected patients is associated with a high level of extranodal involvement [52, 53]. Organs frequently involved are those of the central nervous system and gastrointestinal tract, and the bone marrow. There is a lack of epidemiological data, but small studies have reported the incidence of pulmonary involvement to range from 6% to 31% [53–55]. Primary pulmonary lymphoma is a rare disease reported in small series and case reports in the literature [56, 57]. Pleural effusion may be a secondary manifestation of lymphoma or reflect the presence of a primary effusion lymphoma (PEL). PEL is a rare lymphoma that occurs virtually only in HIV patients and is associated with cavity effusion [58].

The radiological presentation of pulmonary non-Hodgkin lymphoma is often multiple peripheral nodules or masses, in some cases with cavitary lesions and less frequently with pleural effusion or lymph node enlargement [54, 57, 59]. Micronodular infiltrates and alveolar

opacities may occur in rare cases of indolent primary pulmonary lymphoma [54, 59, 60]. Enlargement of lymphoma nodes raises the differential diagnosis of reactive adenopathy. A retrospective report suggested that higher metabolic activity and asymmetric fluorodeoxyglucose uptake by lymph nodes are suggestive of lymphoma [61].

Because of the nonspecific imaging findings and atypical clinical symptoms, diagnosis of non-Hodgkin lymphoma may be delayed. Thus, physicians must be attentive to its pulmonary presentation in HIV patients and in the absence of documented opportunistic infections, biopsy should be performed to exclude malignancies.

Treatment and prognosis

Prior to ART, the prognosis of non-Hodgkin lymphoma in HIV-positive individuals was dependent on the patient’s characteristics: PS, CD4⁺ cell count, history of AIDS, bone marrow involvement, intravenous drug use and age [62, 63]. In the ART era, prognosis of the disease depends of the characteristics of the tumour. Burkitt lymphoma and higher International Prognostic Index score are associated with a lower level of complete remission and worse survival [64, 65].

In the ART era, the recommendations concerning treatment (table 3) are to treat HIV lymphoma patients similarly to the general population.

For treatment of DLBCL, different phase 2 studies have reported an increase in complete remission and overall survival with combination of rituximab (R) with different chemotherapy schedules: CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), EPOCH (etoposide, cyclophosphamide, doxorubicin, vincristine and prednisone) and CDE (cyclophosphamide, doxorubicin and etoposide) [66–70]. A pooled analysis showed a survival advantage of R-EPOCH over R-CHOP (HR 0.38, 95% CI 0.21–0.69; p<0.01) [71].

Table 3. Recommendations for HIV-associated lymphoma

Assessment of the lymphoma

Should include brain and CSF evaluation

Evaluation of HIV

- HIV load and CD4⁺ cell count
- Comorbidity and AIDS history
- Viral co-infection (HCV and HBV)

ART

- Start or continue treatment with particular attention to drug interactions
- Some patients with well-controlled HIV infection may stop ART until the end of chemotherapy

Supportive care

- Infectious prophylaxis
- Haematopoietic growth factors
- Prophylaxis of tumour lysis syndrome

Chemotherapy

- Treat with standard and optimal treatment
- In Burkitt lymphoma and DLBCL give CNS prophylaxis
- With low CD4⁺ count (<50 cells·µL⁻¹), take care for infectious complications and major supportive care

CSF: cerebrospinal fluid; DLBCL: diffuse large B-cell lymphoma; CNS: central nervous system.

Despite the absence of phase 3 trials, R-EPOCH is generally recommended as the first-line treatment. However, in patients with very low CD4⁺ cell count, addition of rituximab remains a matter of debate. A phase 3 randomised trial comparing R-CHOP to CHOP did not demonstrate an advantage in survival, principally due to an increase in infectious death in the R-CHOP arm (14% *versus* 2%). This high incidence was seen particularly in patients with CD4⁺ cell count <50 cells·μL⁻¹ [72]. A recent pooled analysis of 19 prospective trials confirmed the potential interest of adding rituximab to chemotherapy in terms of progression-free (HR 0.50, 95% CI 0.34–0.73; *p*<0.001) and overall survival (HR 0.51, 95% CI 0.38–0.71; *p*<0.0001), but this benefit was not found in patients with CD4⁺ lymphocyte counts below 50 cells·μL⁻¹ [73]. However, this observation was not found in an observational study that reported a benefit of rituximab even in severely immunosuppressed patients [74]. Until the results of a randomised prospective trial are available, administration of rituximab in patients with very low CD4⁺ cell count should be accompanied by vigorous supportive care.

Burkitt lymphoma in HIV patients is no more associated with poor prognosis than in HIV-negative individuals. A recent study reported that a short course of EPOCH with a double dose of rituximab had a progression-free survival rate of 100% and overall survival of 90% at a median follow-up of 73 months [75]. Phase 2 trials and observational studies support the fact that intensive treatment protocols are also feasible but associated with an increase in toxicity and infectious complications [76].

The incidence and the prognosis of PEL and plasmablastic lymphoma remained unchanged [58, 77, 78]. In the absence of standard care, in these poor-prognosis diseases, EPOCH and CHOP treatments are often administered [79, 80].

In the setting of Hodgkin lymphoma, several studies have reported that HIV-infected patients treated with standard ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) therapy have a prognosis close to that of HIV-negative patients [81]. HIV-associated Hodgkin lymphoma has a higher frequency of advanced-stage lymphoma than non-HIV-associated lymphoma. A prospective, nonrandomised trial reported the feasibility of an aggressive BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) regimen with a high complete remission rate of 86% and 2-year overall survival of 86.4% [82].

Supportive care should be part of the treatment, with vigorous anti-infectious prophylaxis and haematopoietic growth factors. Particular attention should be paid to the interaction between ART and chemotherapy, especially for vinblastine, which has been reported to increase haematological and neurological toxicity [83, 84]. Most guidelines recommend continuing ART during chemotherapy. This is based on studies that reported a worse prognosis in patients with high HIV viral load and low CD4⁺ cell count [73, 85], but some experts suggest stopping ART in patients with controlled HIV disease. The goal of this is to avoid drug interactions, which may increase toxicity, and the risk of multiple arrests of ART, which is associated with increase resistance risk [80]. In any case, the choice of ART has to be discussed with HIV experts before chemotherapy.

In conclusion, presentation of lymphoma in HIV-infected patients differs from that in the general population. With ART, the prognosis has been improved for a majority of patients. Although phase 3 trials are lacking, it is recommended to treat HIV-associated lymphoma with the same chemotherapy regimen as non-HIV patients.

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Chronic obstructive lung diseases

Engi F. Attia and Kristina Crothers

As ART access expands in low- and middle-income countries (LMICs), HIV-infected individuals are anticipated to experience prolonged survival along with a greater burden of chronic obstructive lung diseases, similar to increases observed among HIV-infected cohorts in high-income nations. COPD related to cigarette smoking is the major aetiology of chronic obstructive lung diseases in adults living with HIV in high-income countries but the pathophysiology of chronic lung diseases is less well understood in LMICs. The distribution of exposure to risk factors for obstructive chronic lung diseases, such as tobacco smoking and other substance use, indoor biomass burning, and occupational and environmental pollutants, varies across LMICs and high-income countries. A better understanding of the risk factors for chronic obstructive lung diseases and their management among HIV-infected populations is critical to inform patient care and improve outcomes.

The global burden of chronic noncommunicable diseases is growing, chronic obstructive lung diseases (namely COPD and asthma) have emerged as important contributors of morbidity and mortality worldwide [1, 2]. The 2014 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy defines COPD as “a common preventable and treatable disease that is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases” [3]. This chronic airflow obstruction is further characterised by bronchiolitis, parenchymal destruction and goblet cell hyperplasia with excessive mucus production. Asthma is defined as a chronic inflammatory disease of the airways that results in episodic and recurrent cough, wheeze, chest tightness and dyspnoea, triggered by stimuli including allergens, chemical irritants and tobacco smoke [4].

Concomitantly, therapies for HIV have resulted in prolonged survival amongst HIV-infected populations, with an ensuing complex interplay between HIV and chronic lung disease [5, 6]. In this chapter, we review the global epidemiology of and risk factors for chronic obstructive lung diseases among HIV-infected individuals, with a primary focus on COPD, briefly commenting on asthma. We also discuss general considerations for clinical management of HIV-infected patients with these chronic lung diseases.

Global distribution of HIV and chronic noncommunicable diseases

Of the 35 million people living with HIV worldwide, the majority live in low- and middle-income countries (LMICs): 25 million reside in sub-Saharan Africa, nearly 5 million in

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south-east Asia and 1.5 million in Latin America [7]. 99% of the estimated 3.3 million HIV-infected children and adolescents live in these LMICs [7, 8]. Introduction of ART in the mid-1990s has resulted in prolonged survival [5, 6] and has been credited with saving 14 million life-years in LMICs despite limited access [7, 9]. The 9.7 million people receiving ART in LMICs represent only 34% of HIV-infected individuals eligible for ART based on 2013 World Health Organization (WHO) guidelines [7, 10].

As access to ART expands, chronic noncommunicable diseases and age-related disability are likely to increase among HIV-infected individuals in LMICs as they have in high-income countries [6]. Chronic diseases were the leading cause of death in all but low-income countries in 2005 and are projected to emerge as the leading cause of death in all countries by 2015 [1]. Indeed, of deaths attributed to chronic diseases, 80% occur in LMICs, accounting for twice as many deaths as all infectious diseases, including HIV/AIDS, TB and malaria [1, 2].

Chronic lung diseases, including COPD and asthma, are responsible for 7% of deaths and nearly 5% of disability-adjusted life-years (DALYs) worldwide (fig. 1) [2]. COPD alone contributes two-thirds of chronic lung disease DALYs, representing the ninth highest number of DALYs globally in 2010, and is projected to become the seventh highest contributor by 2030 [2, 11]. The impact of chronic lung diseases is probably underestimated given under-recognition and underdiagnosis of these diseases, particularly in LMICs [2, 11–17].

COPD prevalence estimates vary broadly from ~4% to 25% among HIV-uninfected populations worldwide [15–21]. Differences in prevalence amongst high-income countries are primarily attributed to use of different definitions of COPD, and varying distribution of age and risk factors in and across target populations [16, 22]. In LMICs, however, limited availability of resources for conducting population-based surveys and pulmonary function testing hinder true estimation of COPD prevalence, resulting in estimates based on mathematical modelling and expert opinion [12, 14, 15, 23, 24]. Data from general

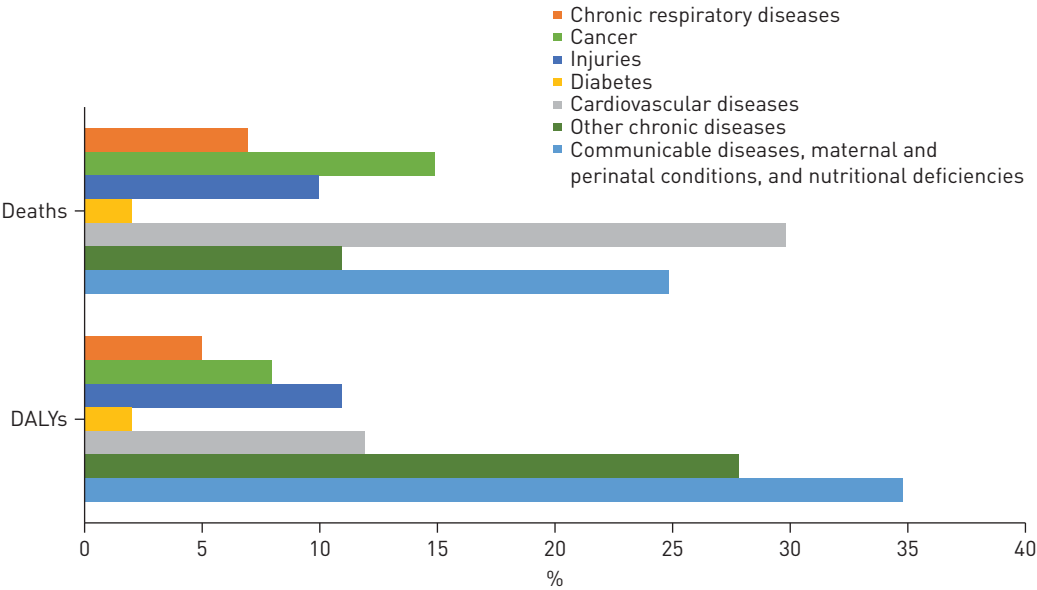


Figure 1. Main causes of death and disability-adjusted life-years (DALYs) worldwide in 2010 based on the Global Burden of Disease Study [11, 12]. 53 million deaths occurred in 2010.

populations of LMICs project that increases in COPD prevalence, morbidity and mortality will be most dramatic in Asian and African countries over the next 20 years, primarily attributed to a progressive rise in tobacco smoking, widespread use of biomass fuels and poor air quality [15].

Additionally, extrapolations from questionnaire-based data suggest that 300 million individuals worldwide have asthma and prevalence is expected to increase as more LMICs become increasingly urbanised. Asthma tends to be more prevalent in urban settings worldwide [25, 26]. Globally, 250 000 deaths per year are attributed to improperly treated asthma and evidence suggests that mortality is concentrated in LMICs lacking access to appropriate therapy [2, 27].

Epidemiology of chronic obstructive lung diseases in HIV

High-income countries

Widespread use of ART and resulting longer life expectancy have shifted the epidemiology of HIV-related pulmonary complications to reflect a greater burden of age-related and chronic noncommunicable comorbid diseases in high-income countries. The burden of chronic obstructive lung diseases in HIV-infected cohorts has been described using clinical, physiological and radiographic measures throughout the HIV epidemic. COPD has been documented to be the major aetiology of chronic obstructive lung diseases in adults living with HIV [28, 29].

COPD

Prior to the advent of cART, radiographic evidence of emphysematous, bullous or cystic lung disease was observed in 40% of patients with a prior history of AIDS-related pulmonary infections [30, 31]. However, DIAZ *et al.* [32] reported a 15% prevalence of emphysema among HIV-infected individuals without prior AIDS-related pulmonary complications compared with 2% of HIV-uninfected participants, suggesting an independent association between HIV infection and emphysema. Indeed, a significant proportion of HIV-infected persons who have not developed AIDS-related pulmonary complications have impaired pulmonary diffusing capacity of the lung for carbon monoxide (DLCO) without significant obstructive or restrictive ventilatory defects, which probably represent early emphysema [33, 34]. In addition to contributing longitudinal pulmonary function data from nearly 1300 participants, the Pulmonary Complications of HIV Infection Study also found an increased prevalence of respiratory symptoms among HIV-infected individuals [34]. A subsequent study found that 25% of HIV-infected individuals reported symptoms consistent with clinical criteria for chronic bronchitis, compared with 12% of uninfected participants [35].

COPD, pulmonary function abnormalities and respiratory symptoms remain common among HIV-infected individuals during the contemporary ART era. In the Veterans Aging Cohort Study (VACS) evaluating 33 420 HIV-infected and 66 840 HIV-uninfected individuals matched by age, sex and race/ethnicity, COPD was the most commonly diagnosed chronic lung disease based on International Classification of Diseases, Ninth Edition (ICD-9) diagnosis codes and 16% of HIV-infected individuals had baseline or incident COPD diagnoses. Those with HIV had a significantly higher rate of COPD diagnoses compared with HIV-uninfected individuals (20.3 *versus* 17.5 per 1000 person-years) [36]. In a subset of VACS that included 1014 HIV-infected and 713 HIV-uninfected men, self-reported COPD prevalence was significantly higher among the HIV-infected group

than the uninfected group (15% *versus* 12%); those with HIV were younger and had fewer pack-years of smoking than their uninfected counterparts. After adjusting for risk factors including age, cigarette smoking and other substance abuse, HIV-infected subjects were 50–60% more likely to have COPD [29]. Additionally, studies conducted in outpatient cohorts of HIV-infected individuals without acute respiratory symptoms illustrate an increased prevalence of airflow obstruction ($FEV_1/FVC < 0.7$, by GOLD criteria), impaired DLCO and chronic respiratory symptoms (table 1) [37–48].

Asthma and airway hyperreactivity

Asthma and airway hyperreactivity have been inconsistently linked to HIV infection in cohort studies conducted in high-income countries during the early ART era, though respiratory symptoms were frequently reported. Several studies suggest that airway hyperreactivity was common among individuals with advanced HIV or opportunistic pulmonary infections [50]. However, when excluding those with prior opportunistic infections, the Pulmonary Complications of HIV Infection Study did not detect a difference in prevalence of airway hyperreactivity between HIV-infected and -uninfected participants; notably, 60% of HIV-infected participants who had a history of asthma demonstrated airway hyperreactivity compared to 16% of those who did not report asthma [51]. A subsequent study comparing asthma prevalence in 20–44-year-old HIV-infected men to that of a randomly selected population of adults found that those with HIV had significantly more airway hyperreactivity (26% *versus* 14%) and wheezing (54% *versus* 21%) [52].

Few studies have assessed the frequency of asthma in HIV-infected adults during the contemporary ART era [53]. Self-reported asthma diagnoses, commonly employed in epidemiological studies, have suggested a prevalence from 11% to 21% among HIV-infected individuals [39, 54] in contrast to a 9% prevalence in the general population [55]. Using spirometry, these studies found bronchodilator reversibility among 4% and 9% of their respective HIV-infected cohorts. Using ICD-9 codes, asthma was the second most common pulmonary diagnosis in VACS, with an incidence of 5.6 per 1000 person-years, with no difference between HIV-infected and -uninfected participants [36]. Further epidemiological studies employing standardised ascertainment of asthma and airway hyperreactivity are necessary to better understand the disease burden in HIV-infected individuals.

Low- and middle-income countries

It is less well understood if there is a similar spectrum shift to a greater prevalence of noncommunicable, chronic pulmonary complications in LMICs, where risk of bacterial pneumonia, TB and PCP among HIV-infected individuals remains persistently high [6, 56, 57]. Though studies are underway, sparse availability of spirometry in research and clinical settings [22, 24] contributes to the paucity of prevalence data for chronic obstructive lung diseases from HIV-infected individuals in African, Asian and Latin American regions, regions that have the greatest HIV prevalence [7, 14, 15, 23].

Two African studies conducted among HIV-infected individuals prior to the WHO-driven scale-up of ART access in LMICs reported >50% prevalence of respiratory symptoms [58, 59]. ONYEDUM *et al.* [49] published one of the few existing contemporary studies determining the prevalence of pulmonary function abnormalities among HIV-infected individuals in LMICs. They found that HIV was an independent risk factor for impaired lung function. Spirometry was performed in 100 HIV-infected Nigerian never-smokers who were not on ART, and 100 age-, sex- and height-matched HIV-uninfected controls; individuals exposed to

Table 1. Studies of pulmonary function among HIV-infected individuals in the contemporary ART era

First author [ref.]	Year	Design/population	Important findings and risk factors
GEORGE [37]	2009	Cross-sectional analysis Spirometry from 234 HIV-infected outpatients from an HIV clinic (Los Angeles, CA, USA)	31% of participants endorsed ≥ 1 respiratory symptom FEV ₁ /FVC <0.7 among 6.8% of participants FEV ₁ /FVC below the age-adjusted lower limit of normal among 8.6% Greater severity of airflow obstruction (FEV ₁ /FVC <0.7) with older age, more pack-years of cigarette smoking, bacterial pneumonia history, ART use FEV ₁ /FVC <0.7: ~35% of <i>Pneumocystis</i> -colonised participants ~5% of noncolonised Respiratory symptoms: 36% of colonised 16% of noncolonised Abnormal lung function in 20% COPD in 3% (all smokers) Asthma in 4% Restrictive ventilatory defect in 8% 53% endorsed ≥ 1 respiratory symptom Smoking associated with cough, sputum and breathlessness after adjusting for ART use 47% of participants endorsed ≥ 1 respiratory symptom 21% had irreversible airflow obstruction 64% of cohort had DLCO <80% pred [47% of never-smokers had DLCO <80% pred] FEV ₁ /FVC <0.7 associated with more pack-years of cigarette smoking, intravenous drug use, ART use FEV ₁ /FVC <0.7 (and FEV ₁ <80% pred) among 16% of participants SGRQ mean score: 7 Smokers: n=17 FEV ₁ /FVC <0.7 among 27.7% of participants FEV ₁ /FVC <0.7 associated with smoking, greater age, PCP FEV ₁ <80% pred among 45% of participants Of ART-naïve participants with CD4 ⁺ count ≥ 350 cells· μL^{-1} , 44% had clinical evidence of chronic lung disease and 28% had abnormal HPCT scan [69% of participants were on ART] Did not detect an association between FEV ₁ and duration of ART or current CD4 ⁺ cell count
MORRIS [38]	2009	Cross-sectional analysis Post-bronchodilator spirometry, sputum induction/oral washes and questionnaires from 42 HIV-infected outpatients (Los Angeles, CA)	Participants with physician-diagnosed asthma had mean: FEV ₁ /FVC 0.69 (versus 0.76 among those without asthma) FEV ₁ 81% pred (versus 96%) DLCO 62% pred (versus 67%) Physician-diagnosed asthma in 21% of participants; bronchodilator reversibility among 9%
Cui [39]	2010	Cross-sectional analysis Pre- and post-bronchodilator spirometry, questionnaire from 119 HIV-infected outpatients from an HIV clinic (Ontario, Canada)	
GINO [40]	2010	Cross-sectional analysis Pre- and post-bronchodilator spirometry and DLCO data from 167 HIV-infected outpatients from an HIV clinic (Pittsburgh, PA, USA)	
HIRANI [41]	2011	Cross-sectional analysis Spirometry, DLCO and SGRQ data from 98 HIV-infected outpatients from an HIV clinic (Philadelphia, PA)	
FERRAND [42]	2012	Cross-sectional analysis Spirometry, oximetry, chest imaging, echocardiography data from 116 adolescent outpatients with vertically acquired HIV (Harare, Zimbabwe)	
GINO [43][#]	2012	Cross-sectional analysis Pre- and post-bronchodilator spirometry, modified SGRQ data from 223 HIV-infected outpatients (Pittsburgh, PA)	

Table 1. Continued

First author [ref.]	Year	Design/population	Important findings and risk factors
KRISTOFFERSEN [44]	2012	Longitudinal analysis Spirometry, DLco data from 88 HIV-infected outpatients; repeated in 63 participants at median follow-up of 4.4 years (Rigshospitalet, Copenhagen, Denmark)	FEV ₁ /FVC <0.7: 10% of participants at baseline 19% at follow-up Impaired average DLco among smokers at baseline Significant (though small) decline in average DLco among smokers and nonsmokers at follow-up Impaired DLco among ~40% of participants at baseline; similar at follow-up FEV ₁ /FVC <0.7 among 14% of participants FEV ₁ /FVC <0.7 among HIV infected associated with HIV RNA >200 000 copies·mL ⁻¹ after adjusting for ART use
DRUMMOND [45]	2012	Cross-sectional analysis Spirometry, clinical, laboratory data from 303 HIV-infected and 774 HIV-uninfected participants with injection drug use (Baltimore, MD, USA)	Did not detect an association between FEV ₁ /FVC <0.7 and HIV status or CD4 ⁺ cell count Mean DLco 66% pred in HIV-infected versus 73% pred in HIV-uninfected women Moderate-to-severe reduction in DLco (≤60%): 37% HIV-infected women 17% HIV-uninfected women
FITZPATRICK [46]	2013	Cross-sectional analysis Pre- and post-bronchodilator spirometry, DLco data and standardised questionnaires from 63 HIV-infected and 36 HIV-uninfected women (San Francisco, CA, USA)	Lower FEV ₁ /FVC associated with history of bacterial pneumonia or PCP Did not detect an association between mean spirometry values and HIV status Mean DLco 69% pred in HIV-infected versus 76% pred in HIV-uninfected men Moderate-to-severe reduction in DLco (≤60%): 30% HIV-infected men 18% HIV-uninfected men
CROTHERS [47]	2013	Cross-sectional analysis Pre- and post-bronchodilator spirometry, DLco data and standardised questionnaires from 300 HIV-infected and 289 HIV-uninfected men (multiple US sites)	Reduced DLco associated with HIV, CD4 ⁺ cell count <200 cells·μL ⁻¹ No significant difference in annual decline in FEV ₁ and FVC between HIV-infected and uninfected overall
DRUMMOND [48]	2013	Longitudinal analysis Serial spirometry from 1064 participants with a history of injecting drugs with or at-risk for HIV infection; ALIVE cohort (Baltimore, MD)	No difference in lung function decline among HIV-infected with well-controlled HIV compared to uninfected Greater rate of decline in FEV ₁ and FVC among HIV-infected participants with HIV RNA >75 000 copies·mL ⁻¹ or CD4 ⁺ cell count <100 cells·μL ⁻¹ compared to HIV uninfected

The study by ONVEDUM *et al.* [49] is not included in this table; although it was conducted during a time period compatible with the contemporary ART era, enrolled participants were not receiving ART. DLco: diffusing capacity of the lung for carbon monoxide; SGRQ: St George's Respiratory Questionnaire; HRCT: high-resolution computed tomography; ALIVE: AIDS Linked to the Intravenous Experience. #: asthma study, other studies in this table addressed COPD.

biomass fuels and occupational dusts were excluded. 32% of HIV-infected individuals had spirometry suggestive of a restrictive ventilatory defect while only 3% demonstrated obstruction; FEV₁ and FVC were significantly lower among HIV-infected compared with -uninfected participants. Cough, breathlessness and wheezing were significantly more common among the HIV infected. Chest radiographs in individuals with respiratory symptoms were normal.

COPD

Though few manuscripts on the prevalence of COPD among HIV-infected individuals living in LMICs have been published to date, emerging data have been presented at several international conferences. Complementing the work of ONYEDUM *et al.* [49], another group in Nigeria reported that the prevalence of COPD, defined by post-bronchodilator FEV₁/FVC <0.7, was 14% among 375 HIV-infected patients attending routine clinic visits, of whom 95% were on ART [60].

Several studies out of South Africa, which is relatively affluent amongst sub-Saharan African countries, have also reported on spirometric abnormalities in HIV-infected individuals. In the Lung-HIV consortium, only 5% out of 917 HIV-infected South Africans demonstrated airflow obstruction based on a pre-bronchodilator FEV₁/FVC <0.7 [61]. Similarly, another study of 152 HIV-infected individuals on stable ART demonstrated irreversible airflow obstruction among 7% [62]. In contrast, a third study found that only one out of 585 HIV-infected participants had airflow obstruction [63]. Differences in prevalence rates among these populations may be partially attributable to the heterogeneous distribution of several COPD risk factors as well as age and ART use.

Asthma and airway hyperreactivity

Asthma and airway hyperreactivity are likely to be emerging problems among HIV-infected populations of LMICs given trends toward increasing urbanisation. However, published data on the epidemiology of asthma in these settings are limited. An ongoing, prospective, longitudinal study in South Africa that aims to describe pulmonary diseases and associated risk factors found that 4% of enrolled participants with HIV reported a history of asthma [63].

Other chronic obstructive lung diseases

Chronic lung diseases and acute pulmonary infections among children <10 years old with vertically acquired HIV have been well-described in LMICs [64, 65]; however, pulmonary complications among adolescents aged 10–18 years have only recently gained attention [42, 66]. Data from southern African countries suggest that up to 36% of HIV-infected infants are “slow progressors”, surviving a median of 16 years in the absence of treatment [67]. These survivors of vertically acquired HIV reach adolescence before being diagnosed with HIV, and studies from Zimbabwe and Kenya suggest that these adolescents carry a high burden of chronic lung disease [42, 67–69]. Obliterative bronchiolitis, an obstructive inflammation and fibrotic obliteration of the airways, was recently documented among adolescents with vertically acquired HIV [42]. As HIV-infected children in LMICs survive into adolescence, many will have lung damage from early infections among other insults. Understanding the prevalence of chronic lung diseases in HIV-infected children and adolescents is critical for developing strategies to mitigate associated morbidity and mortality.

Risk factors for chronic obstructive lung disease in HIV

The complex pathogenesis of chronic obstructive lung diseases in HIV-infected individuals remains unclear and probably involves multiple pathways, including immune, apoptotic,

proteolytic and oxidative stress mechanisms [70–72]. The roles of many risk factors for chronic obstructive lung diseases among the HIV-infected were established largely using data from high-income countries [3]. Here, we further consider data delineating several important risk factors that may be linked to COPD and/or asthma in HIV infection from high-income and LMICs (fig. 2).

HIV infection, immune dysfunction and inflammation

Although the high prevalence of smoking is a clear risk factor for many lung diseases in HIV-infected persons in high-income countries, HIV itself confers an independent risk of chronic lung diseases [6, 49, 57]. COPD, particularly emphysema, has been demonstrated in HIV-infected smokers and nonsmokers [29, 32]. On autopsy, HIV-infected cells have been isolated in emphysematous lung tissue in AIDS patients [73]. In fact, poorly controlled HIV defined by low CD4⁺ cell counts or high HIV RNA levels is associated with worse pulmonary function [36, 45] and greater lung function decline [44, 48]. In the pre-ART era, HIV-infected individuals without clinically apparent pulmonary disease had lower DLCO in association with low CD4⁺ counts [34]. Recent studies demonstrate a similar association where HIV-infected individuals, compared with HIV-uninfected individuals, had significantly lower DLCO despite over 80% of the HIV infected using ART [46, 47].

The role of ART, HIV-related chronic inflammation and immune activation in the risk of chronic lung disease remains unclear. Systemically, treatment with ART decreases HIV

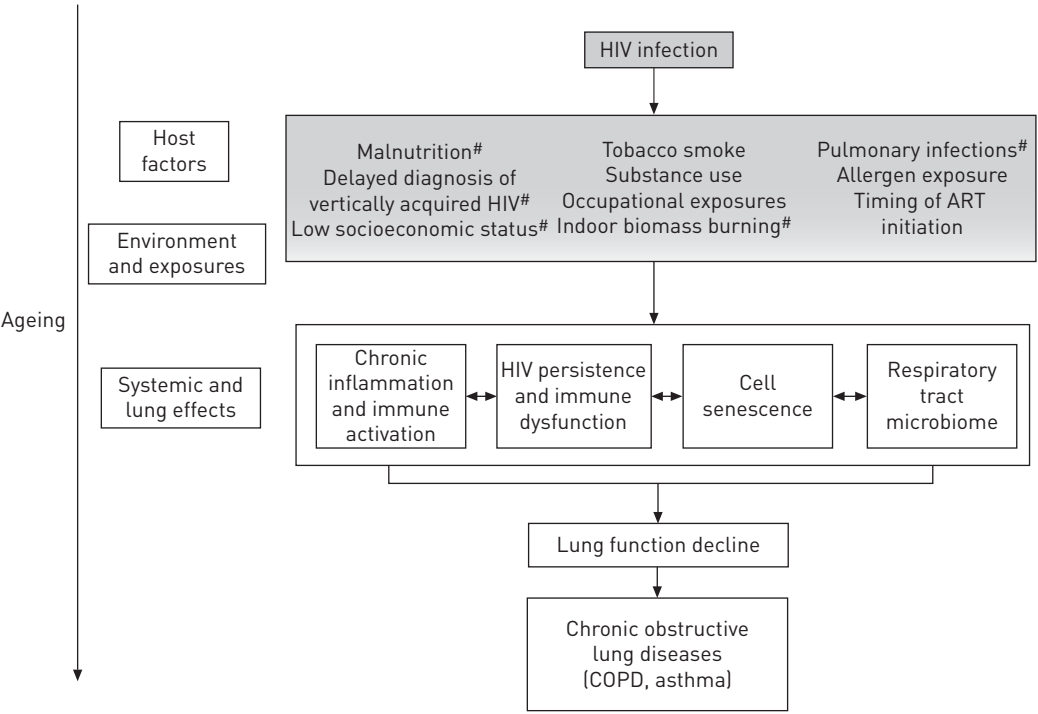


Figure 2. Model for potential risk factors that may be involved in the pathogenesis of chronic obstructive lung diseases among HIV-infected individuals. Exposure to risk factors in the context of ageing varies across low- and middle-income countries (LMICs) and high-income countries, with factors contributing differentially to impact lung function decline and the development of chronic obstructive lung diseases. #: more frequently encountered in LMICs. Reproduced and modified from [36] with permission from the publisher.

replication, chronic inflammation and immune activation, and increases CD4⁺ cell counts. Within the alveolar space, ART similarly decreases pulmonary HIV load and inflammatory responses [74]. Nonetheless, immune activation and chronic inflammation can persist, particularly in those who initiated ART at lower CD4⁺ counts or had treatment interruptions [55, 75]. ART use has not been consistently associated with airflow obstruction in cross-sectional studies [37, 40]. The effects of immune restoration with ART on lung function are not fully understood.

Delayed HIV diagnosis and ART initiation at low CD4⁺ cell counts may result in a greater risk of end-organ injury and development of comorbid conditions, including chronic lung disease [42, 76, 77]. In a recent study, HIV-infected individuals with a nadir CD4⁺ count <200 cells·μL⁻¹ and elevated soluble CD14 were more likely to have radiographic emphysema [78]. A low nadir CD4⁺ may induce incompletely reversible defects in immune function [79] and may be a marker for greater likelihood of pulmonary opportunistic infections. Elevated levels of soluble CD14 may reflect greater immune activation, potentially as a result of mucosal translocation of microbial products, including lipopolysaccharide, despite ART [80–84].

Longitudinal studies of chronic lung diseases in HIV-infected individuals in the recent ART era are emerging. A recent study found that HIV-infected patients may have an increased risk of acute exacerbations of COPD [85]. Furthermore, lung function decline may be more rapid in HIV-infected individuals with low CD4⁺ and higher HIV RNA levels, compared with those with better-controlled HIV and uninfected individuals [48, 86, 87].

Ageing

Increasing age has been associated with risk of COPD in the general population and, more recently, among HIV-infected individuals in high-income countries [29, 88]. Combined with longer exposure to smoking and HIV [89], the natural effects of ageing, accelerated cellular senescence and associated inflammation in HIV contribute to this increased risk; recent reviews of data from high-income countries outline hypothesised mechanisms [88, 90, 91]. It is estimated that >30% of HIV-infected individuals in the USA are over 50 years old and this proportion is projected to rise to 50% by 2020 [92]. Although the mean age of HIV-infected cohorts in LMICs is approximately 35–40 years [62, 63], data from South Africa suggest that older age is associated with airflow obstruction [61, 93].

Cigarette smoke, biomass fuels and other noxious exposures

Traditional risk factors for chronic lung diseases, including tobacco smoking and occupational exposure to dusts and fumes, are important co-factors that contribute to risk for chronic obstructive lung diseases amongst HIV-infected populations. These factors probably also contribute to chronic obstructive lung diseases in LMICs as they do in high-income countries [24, 94].

Tobacco smoking is the most important causal factor of COPD and is more common among HIV-infected than general populations in high-income countries [95]. Studies in the USA have reported that up to 75% of HIV-infected participants have ever smoked and ~40–50% are current smokers [36, 37, 95, 96]. Although data suggest an increasing smoking prevalence in LMICs [15], it is not clear whether rates of smoking are also disparately higher amongst HIV-infected compared with -uninfected individuals in these countries.

Additional risk factors for COPD that are generally more prevalent among HIV-infected individuals in high-income countries include inhaled and intravenous drug use (IDU) [29, 34–36, 40]. Mixed data describe the association of airflow obstruction with inhaled marijuana, cocaine and heroin in these settings [97–99]. Similarly, IDU, particularly of methylphenidate, has been associated with development of precocious emphysema [97]. In a cohort of intravenous drug abusers, 17% of HIV-infected participants had airflow obstruction [45].

Less is known about the impact of illicit inhaled or intravenous substances on risk for chronic lung diseases among HIV-infected populations in LMICs. In South Africa, smoking marijuana in combination with the sedative agent methaqualone (Mandrax) has been linked with respiratory symptoms and airway abnormalities amongst HIV-uninfected persons [100]. Smoking “whoonga”, often a combination of antiretroviral medications, illicit drugs, household products and/or rat poison, has been described in HIV-infected and uninfected persons [101, 102]. Recreational use of ART for its psychoactive effects, both *via* smoking and ingestion, has been reported in South Africa and regions of the USA [101–104].

Burning of biomass fuel is an important risk factor for chronic obstructive lung diseases in resource-limited settings. More than 3 billion people worldwide burn solid biomass fuels, including coal, wood, paraffin, and animal and crop waste, for cooking, heating and other energy needs, and usage is upward of 75% in many African and south-east Asian countries [105–107]. Indoor burning of biomass emits high levels of pollutants, similar to those in tobacco smoke [108]. Cross-sectional studies have demonstrated significant associations of indoor biomass burning with respiratory symptoms, impaired lung function and COPD in Africa, Latin America and south-east Asia, particularly among women in rural settings [107–112]. A dose–response relationship with the duration and magnitude of exposure is recognised [109]. The impact of indoor biomass burning may be compounded among the HIV infected given their greater susceptibility to pneumonia and chronic lung diseases [105, 107].

Exposure to occupational dusts, gases, fumes and smoke is linked to the development of COPD and asthma, based on numerous epidemiological studies conducted in various settings worldwide [24, 108]. The population-attributable risk for the contribution of workplace exposures to both COPD and asthma is estimated to be on the order of 15–20% in high-income countries [113]. In both of these chronic obstructive lung diseases, cigarette smoking appears to modify risk [108, 113]. However, the attributable risk associated with occupational exposures for chronic obstructive lung diseases has not been specifically investigated in HIV-infected populations in either high-income countries or LMICs.

Pulmonary infections

Indolent and acute pulmonary infections are associated with an increased risk of pulmonary function abnormalities and COPD among HIV-infected cohorts. In a longitudinal, multisite study following 1149 HIV-infected individuals, PCP and bacterial pneumonia were associated with permanent decreases in FEV₁, FVC, FEV₁/FVC and DLCO [114]. Opportunistic infections may also increase the risk of airway hyperresponsiveness [43]. Acute respiratory infections have been linked to increased levels of HIV RNA in the lung, possibly contributing to lung injury and subsequent pulmonary function decline [115, 116]. For example, KOZIEL *et al.* [115] detected HIV RNA in the lungs of 67% of HIV-infected individuals with active pulmonary infections compared with 16% of asymptomatic subjects.

Pulmonary colonisation with microorganisms in the absence of overt pneumonia may also play an important role in COPD pathogenesis. In a study of HIV-infected patients, those who had *Pneumocystis jirovecii* colonisation in their respiratory tracts had worse airflow obstruction than those without colonisation, after adjusting for smoking [38]. Notably, 64% of those colonised with *Pneumocystis* were on ART compared with 84% of those who were not colonised.

A systematic review of epidemiological studies from high-income countries and LMICs provides strong evidence for an association between pulmonary TB and chronic airflow obstruction in general populations [117]. This association may be independent of cigarette smoking and exposure to biomass burning [117]. Few studies have examined the impact of HIV on this association. For instance, a study conducted in Indonesia found that HIV infection was independently associated with worse respiratory-related quality of life after completing anti-TB therapy but did not find an association of HIV with airflow obstruction [118]. Several other studies have included participants with HIV but small numbers limit analyses to evaluate the potential confounding of HIV on the association of pulmonary TB and airflow obstruction [117, 119, 120]. HIV, in addition to high smoking rates, malnutrition, overcrowding and burning of biomass fuels, is driving the TB epidemic in many LMICs, resulting in a convergence of the effects of HIV, TB, smoking and COPD on lung health in these settings [94].

Early-life exposures

Although factors, such as low birth weight, indoor/outdoor air pollution, asthma and respiratory infections present early in life have been linked to impaired lung development and lung function in adulthood among general populations [108, 121–123], the impact of vertically acquired HIV on risk for chronic lung disease is not well understood. Incomplete immune reconstitution has been described in vertically acquired HIV [124] and may contribute to development of pulmonary abnormalities. Little is known about potential risk factors for chronic lung disease such as stunted growth and malnutrition amongst those with vertically acquired HIV in high-income countries or LMICs [22, 28, 108].

Management of HIV-infected individuals with chronic obstructive lung diseases

To date, no published studies have investigated the management of chronic obstructive lung diseases specifically in HIV-infected patients in either high-income countries or LMICs. In the absence of such data, management should generally follow guidelines proposed for HIV-uninfected patients where feasible and provided no contraindications exist [3, 4, 125].

COPD and asthma maintenance therapies

The safety and effectiveness of maintenance therapies for both COPD and asthma deserve further study in HIV-infected individuals. Side-effects and toxicities of these medications may potentially be more frequent among HIV-infected persons, as concomitant multi-morbidity and polypharmacy are common. In particular, providers should be aware of potential complications associated with inhaled corticosteroids. Inhaled corticosteroids may increase the risk for complications that are already present in HIV-infected individuals, including bacterial pneumonia [126, 127], TB [128] and bone loss [126, 129]. In addition,

inhaled corticosteroids can interact with ritonavir and other protease inhibitors, resulting in increased systemic corticosteroid levels [72, 93]. In terms of other COPD maintenance therapies, arrhythmias and acute coronary syndromes may be associated with long-acting β -agonists and muscarinic antagonists [130, 131]. These complications are of potential concern in HIV-infected patients, given the increased risk of cardiovascular disease in these patients [132, 133].

The use of inhaled corticosteroids or other COPD maintenance therapies in HIV-infected individuals with COPD as a sequela of prior pulmonary infections, including TB, has not been evaluated [15]. It is currently unknown whether TB-related lung function impairment has a similar clinical course and response to standard therapies as COPD from other causes, such as tobacco smoking [108, 117].

Smoking cessation

Smoking cessation is of paramount importance in HIV-infected smokers with chronic lung diseases, as current smoking is a leading preventable cause of mortality in HIV-infected individuals in high-income countries and is associated with substantial morbidity [134, 135]. Despite high rates of smoking amongst HIV-infected populations in high-income countries, healthcare providers may be less aware of current smoking and less confident in counselling patients regarding cessation [136]. Many HIV-infected persons report motivation to quit smoking, with 30–70% reporting at least one quit attempt in recent studies [137, 138]. However, many putative barriers to achieving cessation, including concurrent IDU, alcohol abuse and mental health disorders, exist in these HIV-infected populations [138, 139].

Smoking cessation interventions can be effective in HIV-infected populations in high-income countries [139–141], although overall cessation rates remain low. The role of different interventions remains unclear. LLOYD-RICHARDSON *et al.* [142] found that a motivationally enhanced intervention plus nicotine replacement therapy (NRT) was not effective over and above a standard intervention plus NRT. The absolute smoking cessation rate was only ~10% at 6 months in both arms of the study. Smaller studies report modest success with nicotine patches and counselling [141] and use of mobile telephones for counselling [140]. Two open-label studies have demonstrated the potential efficacy, safety and tolerability of varenicline in HIV-infected populations [143, 144], one of which additionally found varenicline to be more effective than NRT amongst HIV-infected smokers [143]. Though limited data suggest that bupropion may be an effective smoking cessation intervention among those with HIV, several potential interactions between ART and bupropion exist [145]. While ritonavir in combination with lopinavir may decrease plasma concentrations of bupropion, other protease inhibitors may increase plasma concentrations to toxic levels, which may manifest as seizures.

As cigarette smoking rates may be rising among HIV-infected individuals in LMICs, a better understanding of strategies for smoking cessation and prevention is needed in these settings. While HIV-infected smokers in high-income countries tend to engage in high-risk behaviours, including alcohol and drug abuse [139], the degree to which this is true and may impact cessation efforts in LMICs is unclear. A recent Brazilian study reported an association of heavy alcohol drinking, marijuana use and sex-specific risk factors with cigarette smoking that may provide potential targets for future smoking cessation interventions in populations with similar characteristics [146].

Pulmonary rehabilitation

HIV-infected individuals with chronic lung disease may benefit from pulmonary rehabilitation. The systemic and skeletal manifestations encountered in HIV-uninfected patients with COPD are also likely to contribute to decrements in physical capacity in patients with HIV. Among HIV-infected US veterans, both COPD and asthma were among the top comorbid conditions independently associated with self-reported physical disability [147]. Chronic airway disease, manifested by cough and decreased FEV₁, was also associated with worse performance on 6-min walk testing in HIV-infected individuals [148].

Pneumonia prevention

Risk of pneumonia is compounded in HIV-infected patients with chronic lung disease. Preventative strategies include pneumococcal vaccines for eligible individuals and yearly influenza vaccine for all HIV-infected individuals. The role for chronic antibiotic therapy to prevent exacerbations of disease or LRTIs in HIV-infected individuals with chronic obstructive lung diseases is unclear. Azithromycin for the prevention of COPD exacerbations may be considered in HIV-infected individuals with more severe COPD and frequent exacerbations who meet criteria used in the trial by ALBERT *et al.* [149]. Prophylactic antibiotics are otherwise reserved for preventing opportunistic infections, as per published guidelines in those who meet criteria, which generally include CD4⁺ count <200 cells·μL⁻¹ [150].

The Practical Approach to Lung Health strategy has been adapted in LMICs with high HIV burden to provide guidance for the management of HIV-related pulmonary diseases to primary care providers who may have little direct experience with addressing these disease processes [151]. Guidelines are tailored to address early identification and treatment of pulmonary infections as well as COPD and asthma among HIV-infected patients with chronic respiratory symptoms, to decrease the morbidity and mortality associated with HIV-related pulmonary diseases in LMICs [2, 151].

Conclusion

As ART access expands in LMICs, HIV-infected individuals are anticipated to experience prolonged survival along with a greater burden of chronic obstructive lung diseases that have increased among HIV-infected cohorts in high-income countries [6, 10]. However, exposure to chronic lung disease risk factors is heterogeneous across these settings. A sustained high incidence of pulmonary infections such as bacterial pneumonia and TB remains a major public health challenge in LMICs despite ART use [6, 57, 152], and sequelae of pulmonary infections may be more likely to contribute to chronic lung diseases by way of permanent declines in lung function [114, 117] in these populations. As smoking gains popularity and countries become more industrialised, a greater impact of tobacco and occupational exposures is also anticipated in LMICs [24]. Although most studies examining the effects of indoor biomass burning have been conducted in LMICs, the risks associated with biomass burning may not be restricted to these countries [153, 154]. As a result of the anticipated increase in chronic obstructive lung diseases among HIV-infected individuals, greater disability and escalation of healthcare needs are likely to ensue worldwide. A better understanding of chronic obstructive lung disease risk factors among those with HIV and related unique management considerations is critical to inform patient care and improve outcomes.

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Interstitial lung disease

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It has been increasingly recognised that patients with HIV infection are at higher risk of noninfectious lung disorders. Of these, the interstitial lung diseases stand out as an important group of disorders for which the pathogenesis is not fully understood, despite significant advances over the past three decades. Lymphocytic interstitial pneumonitis, nonspecific interstitial pneumonitis, organising pneumonia, follicular bronchiolitis, sarcoidosis and drug-induced interstitial lung disorders have been reported in the setting of HIV infection. With the advent of effective cART, it seems that the epidemiology of these diseases is changing. For instance, the prevalence of LIP appears to be declining while other conditions, such as sarcoidosis, may be on the rise. The immunosuppressed state of HIV-infected patients with interstitial lung diseases often creates a conundrum for the clinician, as some of these conditions are treated with immunosuppressants. There is an enormous need for research in this area, as much of the literature remains anecdotal. This should come in the form of investigations exploring viral–host interactions, as well as carefully designed clinical studies.

HIV infection is associated with a number of pulmonary complications that can be broadly categorised as infectious or noninfectious. The epidemiology of these disorders changed with the introduction of effective cART, which helped change HIV into a chronic disease. In the pre-cART era, pulmonary infections were very common. In patients on cART, however, pulmonary infections are less frequent. Noninfectious lung disorders that have been associated with HIV infection include COPD, PH, neoplasms and interstitial lung diseases [1–5]. Of these, the interstitial lung diseases remain an enigmatic group that includes a number of different entities.

Interstitial lung diseases are disorders affecting the lung interstitium or parenchyma where the alveolar units responsible for gas exchange are located. Often, but not always, interstitial lung diseases progress slowly with development and worsening of dyspnoea and exercise intolerance over a period of months and even years. Imaging studies show bilateral lung infiltrations, and physiological derangements related to lung restriction and hypoxaemia are common. Pulmonary function tests are helpful in evaluating the severity of lung dysfunction but are nonspecific and cannot determine a diagnosis by themselves. In addition, some cases present during the acute phase of disease, requiring hospitalisation, and it is not advisable to obtain pulmonary function tests at that time. Consequently, pulmonary function tests are most useful for determining progression of lung dysfunction over time. However, there are

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certain lung physiology patterns that might help in defining the diagnosis and prognosis of patients with chronic illness when other data are available. For example, disorders predominantly affecting the interstitium of the lung will cause a restrictive pattern. Depending on the severity, the diffusion capacity may be decreased, thereby highlighting the need for evaluating oxygenation. Some disorders, however, may predominantly affect the bronchioles leading to airflow limitation and hyperinflation. Also, a mixed obstructive–restrictive disorder is often detected. Tissue histology typically shows inflammation and alterations in lung architecture due to cellular infiltration, and/or excessive connective tissue deposition leading to fibrosis.

Interstitial lung diseases can result from exposure to inorganic agents like asbestos and silica, organic allergens, or drugs like amiodarone. More often than not, however, interstitial lung diseases are of unknown aetiology or are idiopathic. Of these, the idiopathic interstitial pneumonias are the most common. These disorders are best identified by surgical biopsy which allows for careful analysis of patterns of cellular infiltration and tissue destruction. Idiopathic pulmonary fibrosis is the most common idiopathic interstitial pneumonia and is characterised by a specific histological pattern termed usual interstitial pneumonitis. Another histological pattern commonly seen in patients with an idiopathic interstitial pneumonia is nonspecific interstitial pneumonia (NSIP). This pattern can be seen in patients with interstitial lung disease of unknown aetiology or associated with systemic disorders such as connective tissue disorders (e.g. rheumatoid arthritis and polymyositis–dermatomyositis) or hypersensitivity pneumonitis. Interestingly, as will be discussed later, NSIP has been documented in patients with HIV infection. Another histological pattern found in patients with HIV infection is LIP. Although LIP was initially included within the idiopathic interstitial pneumonias, it is now known to occur mainly in patients with connective tissue disorders (e.g. Sjögren’s syndrome) or HIV infection. Thus, HIV has been associated with interstitial lung diseases with histological patterns of NSIP and LIP [3, 6]. Other histological patterns identified in HIV infection include organising pneumonia and granulomatous inflammation, such as that seen in sarcoidosis [7, 8]. Drug-induced interstitial lung disease has also been reported in HIV [9].

It is difficult to quantify the burden of interstitial lung diseases in HIV-infected patients. Early reports suggested a high prevalence of NSIP [3, 10]. These studies relied on histopathology specimens and were based on a select group of patients being investigated in referral centres. However, epidemiological cohort studies point to a less prominent role of interstitial lung diseases as a cause of respiratory disease in HIV-infected patients. As an example, an epidemiological study evaluating the incidence of respiratory diseases in 1143 HIV-infected patients in six urban centres in the USA during a 5-year period found the incidence of NSIP or LIP to be around 0.5 episodes per 100 person-years. In contrast, bacterial pneumonia and PCP accounted for incidences of 5.5 and 5.1 episodes per 100 person-years, respectively [11]. In a more recent prospective cohort study, pulmonary fibrosis was present at baseline in 0.37% of 33 420 HIV-infected patients and in 0.10% of 66 840 HIV-uninfected patients ($p < 0.001$). The incidence of pulmonary fibrosis was 0.9 and 0.6 per 1000 person-years in HIV-infected and HIV-uninfected individuals, respectively ($p < 0.001$). After adjustment for smoking and other factors, HIV infection remained associated with an approximately 79% higher risk of developing lung fibrosis. Unfortunately, the study did not specify the aetiologies of lung fibrosis [4]. Interestingly, the prevalence of LIP appeared to decline after the advent of cART in 1996 [12], while other conditions, such as sarcoidosis and perhaps drug reactions, appear to be on the rise [13, 14].

In this chapter, we present a narrative review of HIV-related interstitial lung diseases focusing on LIP, NSIP, follicular bronchiolitis and organising pneumonia. We also succinctly discuss sarcoidosis, drug-induced pulmonary toxicity and IRIS, given their increasingly recognised importance as a cause of diffuse parenchymal lung disease in HIV-infected patients. The material discussed here mostly pertains to the adult population.

Lymphocytic interstitial pneumonia

LIP is a parenchymal lung disease characterised by diffuse infiltration of the lung by sheets of lymphocytes disrupting the gas exchanging units, and leading to hypoxaemia and dyspnoea. LIP can be seen in rheumatological disorders such as Sjögren’s syndrome. In HIV, LIP is characterised by CD8⁺ lymphocyte infiltration of the lungs in the absence of an opportunistic infection. In some cases, LIP is part of a systemic entity termed diffuse infiltrative lymphocytosis syndrome. Features of the syndrome include chronic sicca symptoms, bilateral salivary gland enlargement and CD8⁺ lymphocytic infiltration of affected organs [12].

Patients with LIP typically present with dyspnoea and cough [15]. Other, less frequent manifestations include sicca syndrome and fever [16]. In 1990, a case series of 17 patients with HIV infection and CD8⁺ lymphocytosis was described; 10 of these patients had LIP confirmed by histology [17]. The chest radiograph findings of LIP included reticulonodular infiltrates often superimposed on patchy alveolar opacities [18]. Changes detected by computed tomography in LIP include ground-glass attenuation, centrilobular nodules, subpleural nodules and occasional cysts [19]. These radiographic abnormalities are often accompanied by physiological derangements detectable by pulmonary function testing and include a restrictive physiology with substantial decreases in carbon monoxide diffusion capacity [6].

The pathogenesis of LIP in HIV is poorly understood but studies have suggested a role for viral–host interactions in the development of altered immune responses, and an imbalance of the lung oxidant and antioxidant systems (table 1). An evaluation of the T-cell antigen receptor gene repertoire of T-cells in lung tissue samples harvested from patients with HIV-related LIP revealed uniform, oligoclonal infiltrating T-cell expansions. Such high-frequency expansion in HIV-infected patients is hypothesised to be antigen driven and perhaps unique to HIV, as it was not present in patients with LIP related to EBV infection [20]. In evaluating lung biopsy specimens from 50 HIV-infected patients diagnosed with NSIP or LIP, HIV RNA expression was found in cells of some of these patients, while expression of EBV or CMV was not detected by *in situ* hybridisation [21]. In patients with diffuse infiltrative lymphocytosis syndrome, HIV-1 gp120 antigens are found in the macrophages adjacent to the lymphoid aggregates, which suggests that circulating monocytes harbouring HIV-1 enter the tissues and

Table 1. Interstitial lung disorders associated with HIV infection according to pathogenesis

Conditions where viral–host interactions are likely to play a major role

- LIP
- Nonspecific interstitial pneumonia
- Follicular bronchiolitis

Conditions where immune restoration is likely to play a major role

- Sarcoidosis
- Some drug-induced reactions (e.g. paradoxical worsening in patients being treated for opportunistic infection)

interact with lymphocytes. The CD8⁺ T-cells that infiltrate the tissues of these patients show surface expression of antigens, denoting a memory phenotype. These findings suggest that the observed tissue CD8⁺ lymphocytosis is triggered by antigen exposure [17]. In another study, analysis of cells obtained *via* bronchoalveolar lavage of HIV-infected patients with LIP demonstrated the presence of HIV in alveolar macrophages, as determined by hybridisation, and showed cytotoxicity by CD8⁺ lymphocytes upon interaction with HIV-infected autologous macrophages as determined in a cytotoxicity assay [22]. Another study evaluating cells harvested *via* bronchoalveolar lavage from humans infected with HIV-1 demonstrated that the alveolitis associated with HIV-1 infection is predominantly caused by CD8⁺ lymphocytes with overexpression of the TNF receptor family member CD120b. This study, however, did not restrict the analysis to patients with idiopathic interstitial pneumonias [23].

A role for an imbalance between the oxidant and antioxidant systems in virus-related idiopathic interstitial pneumonias is highlighted by a study in which lambs were inoculated with *visna-maedi* virus, a lentivirus that produces a pneumonitis that resembles that caused by HIV-1. Most of the virus-inoculated lambs developed a lymphocytic infiltrate and peribronchovascular lymphoid nodules. Upon stimulation, hydrogen peroxide production by alveolar macrophages was increased in the virus-inoculated lambs as compared with controls [24]. Furthermore, in a study of patients with HIV infection, those on ART were found to have higher levels of the antioxidant glutathione in the bronchoalveolar lavage fluid as compared with those not on ART after adjustment for age and body mass index. This study did not attempt to correlate the oxidative stress with development of lung disease. In fact, an inclusion criterion for the study was normal spirometry [25].

The diagnosis of LIP is usually established by transbronchial or surgical lung biopsy after exclusion of opportunistic lung infection. The pathology specimens typically reveal lymphoid interstitial infiltrates with marked alveolar septal distribution. Other distribution patterns include peribronchiolar, perivascular and pleural patterns. Lymphoid aggregates and type II pneumocyte hyperplasia are often seen. Immunohistochemistry shows a preponderance of T-cells [21].

The recommended treatment for LIP is cART, as it appears that the condition is caused by uncontrolled virus replication. This may explain the observed decrease in the prevalence of HIV-related LIP in the cART era. A retrospective analysis of HIV-infected patients referred to a rheumatology clinic in Houston, TX, USA, found a significant reduction of cases of LIP over time. From 1994 to 1997, before cART was introduced to patients in that location, 32 patients with LIP were seen, whereas only three cases were identified from 1998 to 2003 [12]. This, coupled with case reports showing improvement of LIP with cART, strengthen this recommendation. Without treatment, the prognosis is varied [26]. However, the prognosis tends to be favourable with cART [16].

Nonspecific interstitial pneumonia

Like LIP, NSIP was first described in patients with idiopathic interstitial pneumonia and is characterised by diffuse infiltration of the lung by immune cells. As such, NSIP is considered by some experts to represent a milder form of LIP [21]. In this context, both NSIP and LIP may represent extremes of the same disease spectrum. In the absence of tissue biopsy, a distinction between NSIP and LIP can tentatively be made on the basis of epidemiological features and associated clinical manifestations (table 2).

Table 2. Characteristics of interstitial lung disorders associated with HIV infection

	Clinical manifestations	Immune status	Radiological findings	Pathology	Treatment
NSIP	Cough, fever, and dyspnoea More common in adults	CD4 ⁺ T-cell count often >200 cells·µL ⁻¹	Chest radiography: bilateral interstitial infiltrates	Lymphoid infiltrate with predilection for the peribronchiolar or perivascular areas	Oral corticosteroids might be beneficial
LIP	Dyspnoea and cough Less frequently, sicca syndrome and fever More common in children	CD4 ⁺ count upon presentation varies	Chest radiography: reticulonodular infiltrates with or without patchy alveolar opacities	Lymphoid interstitial infiltrates with marked alveolar septal distribution	cART
Follicular bronchiolitis	Weight loss Fever Shortness of breath Cough	CD4 ⁺ count upon presentation may vary	Chest radiography: often nonspecific CT: centrilobular nodules	Peribronchial lymphocytic infiltrate with germinal centres	cART
Organising pneumonia	Dyspnoea Cough Fever	CD4 ⁺ count often <200 cells·µL ⁻¹	Chest radiography: alveolar infiltrates and nodular opacities	Intraluminal organising fibrosis in the distal airspaces Patchy distribution Preserved lung architecture Uniform temporal appearance Mild interstitial inflammation Noncaseating granulomas	Oral corticosteroids
Sarcoidosis	Dyspnoea Cough Cervical or axillary adenopathy Less often uveitis, erythema nodosum, fever and skin nodules	CD4 ⁺ count often <200 cells·µL ⁻¹	Chest radiography: hilar/mediastinal adenopathy and/or parenchymal nodules		Oral corticosteroids in selected cases
Drug-induced pulmonary toxicity	Dyspnoea Cough Skin rash Fever	CD4 ⁺ count upon presentation varies	Chest radiography: bilateral interstitial infiltrate	May vary according to the type of reaction	Discontinuation of the offending medication

NSIP: nonspecific interstitial pneumonia; CT: computed tomography.

Although there is a scarcity of data regarding the true prevalence of NSIP in HIV-infected patients, an early investigation suggested a staggeringly high figure. Between 1982 and 1986, the National Institutes of Health Clinic Center (Bethesda, MD, USA) evaluated 110 patients with AIDS and pulmonary symptoms or abnormal chest radiographs. In this study, NSIP was considered to be present in 41 (38%) patients [3]. In another study, 351 HIV-infected patients underwent bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy for clinical suspicion of PCP. In the 67 patients found not to have PCP, NSIP was the most common diagnosis, accounting for 16 (5%) of the 351 patients with suspected PCP [10]. The variation in prevalence across these studies may stem from different inclusion criteria and baseline patient population characteristics. Another consideration is that many studies in HIV-related lung disease do not include surgical biopsy for analysis of tissue histology. This is important because it is difficult to distinguish NSIP from other idiopathic interstitial pneumonias by transbronchial lung biopsy alone due to the small size of the tissue obtained.

In patients with symptoms related to NSIP, common manifestations include cough, fever and dyspnoea [3]. Differently from patients with LIP, these patients do not typically present with sicca symptoms or bilateral salivary gland enlargement. Also, in distinction to LIP, NSIP predominantly affects adults [21]. Most patients with NSIP and clinical manifestations have normal serum lactate dehydrogenase (LDH) and a CD4⁺ cell count above 200 cells· μL^{-1} [10]. More than half of the patients have abnormal chest radiographs, with bilateral interstitial infiltrates being the most common pattern. The intensity of lung involvement may vary, with some patients developing mild perihilar markings, while others having a more pronounced diffuse infiltrate [27].

It appears that NSIP is asymptomatic in a significant number of patients. In a study of 23 HIV-infected patients with AIDS (based on US Centers for Disease Control and Prevention criteria) or low CD4⁺ lymphocyte count, bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy revealed 11 cases with histological evidence of NSIP [28]. Again, this study was highly limited by the fact that surgical biopsies were not performed.

Like LIP, PCP is a common component of the differential diagnosis for NSIP. Both NSIP and *Pneumocystis* present with respiratory symptoms and interstitial infiltrates on the chest image (fig. 1). Patients with NSIP tend to be less immunosuppressed and have a lower level of serum LDH; however, it is very difficult to distinguish NSIP from PCP on a clinical basis. An initial work-up for a patient in whom these conditions are suspected should include induced sputum followed, if not diagnostic, by bronchoscopy with bronchoalveolar lavage. If these tests do not reveal an aetiology, a lung tissue specimen should be pursued. Ultimately, the diagnosis of NSIP is one of exclusion and established by histological assessment of a specimen obtained preferably by surgical lung biopsy. However, transbronchial lung biopsy is often favoured because it is less invasive. In the series described by TRAVIS *et al.* [21], the most common histological characteristic included a lymphoid infiltrate with predilection for the peribronchiolar or perivascular areas. Lymphoid aggregates or germinal centres are seen in a minority of patients. Increased numbers of alveolar macrophages are seen in most patients. The degree of the lymphoid infiltrate is mild to moderate, as opposed to the severe infiltrate typically seen with LIP [21].

Not many studies have reported on the natural history of NSIP. In a series of 16 patients, arterial blood gases were analysed at baseline in all of them and at 7–10 days follow-up in those considered sicker (seven patients). The follow-up blood gas analysis showed substantial improvement in arterial oxygen levels despite no specific therapy for NSIP [10]. In another

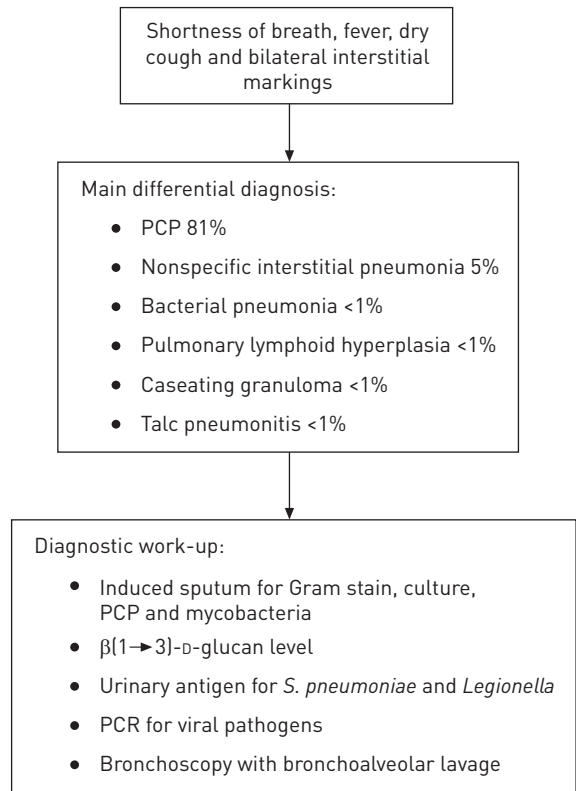


Figure 1. Differential diagnosis and proposed initial work-up for HIV-infected patients with dyspnoea and bilateral interstitial markings. Differential diagnosis is based on the study by SATTLER *et al.* [10]. The study was performed in the era before cART. Patients whose chest radiograph showed pleural effusion, miliary pattern or hilar adenopathy were excluded. *S. pneumoniae*: *Streptococcus pneumoniae*.

series of seven patients seen before the advent of cART, pneumonitis improved with oral corticosteroids in three patients and without treatment in three other patients. Six patients died within 3 years; in none of them was the cause of death clearly attributed to NSIP [29]. In aggregate, these small series suggest a favourable short-term prognosis for patients with NSIP. There are no clinical trials or large case series evaluating treatments for HIV-infected patients with NSIP. Only a few case reports have suggested a potential benefit with oral corticosteroids [29, 30]. The usual mild course of the disease in association with reports of spontaneous resolution suggest that, in general, no specific therapy should be pursued for this condition in the absence of limiting symptoms and/or physiological progression.

Follicular bronchiolitis

Patients with HIV infection may also develop follicular bronchiolitis, which is an interstitial lung disease characterised by lymphocytic infiltrate with germinal centres. An important distinction from LIP is that here the infiltrate is predominantly peribronchial and without intense alveolar septal infiltration [31]. The symptoms may include weight loss, fever, shortness of breath and cough. The chest radiograph may be nonspecific. However, computed tomography shows centrilobular nodules. The cases reported in the literature show good response to cART [32, 33].

Organising pneumonia

Organising pneumonia is a term used to define a clinical–pathological entity characterised on histology by “organization within alveolar ducts and alveoli (‘organizing pneumonia’) with or without organization within bronchioles (‘polypoid bronchiolitis obliterans’)” [31]. Organising pneumonia can be idiopathic, in which case it is called cryptogenic organising pneumonia, or associated with a number of conditions, in which case it is termed organised pneumonia with a modifier such as organising pneumonia associated with radiation therapy [34].

A few cases of organising pneumonia have been described in association with HIV infection [8, 35–37]. Patients with organising pneumonia typically present with dyspnoea, cough and fever. On physical examination, crackles are often identified upon auscultation [8]. KHATER *et al.* [35] performed an analysis of 11 cases reported in the literature; all except one were male. Most had AIDS and their CD4⁺ count was generally, low ranging from 2 to 214 cells·μL⁻¹ [35]. However, a more recent study described a patient with a CD4⁺ count above 500 cells·μL⁻¹ who had a concomitant diagnosis of HIV infection and organising pneumonia [36]. The most common radiographic patterns included bilateral alveolar infiltrates followed by nodular opacities [8, 35].

Because organising pneumonia can present acutely and with alveolar consolidation on the chest radiograph, CAP is often initially entertained in the differential diagnosis. Some other conditions that can clinically mimic organising pneumonia include NSIP, hypersensitivity pneumonitis, eosinophilic pneumonia and pulmonary lymphoma. When it presents as a nodular opacity, lung cancer is often considered. It is also important to realise that the organising pneumonia pattern on histopathology analysis is not specific and can be seen in a number of conditions, such as lung infection, hypersensitivity pneumonitis, pulmonary vasculitis and lymphoproliferative disorders [38]. Thus, caution should be exercised when interpreting the results of lung histopathology specimens revealing an organising pneumonia pattern. Sufficient tissue must be obtained to confidently exclude conditions that are in the pathological differential diagnosis. Taking this into consideration, the diagnosis of organising pneumonia is eventually established by the analysis of a lung histopathology specimen revealing an organising pneumonia pattern. According to the American Thoracic Society/European Respiratory Society joint statement, the characteristic histopathology features of organising pneumonia pattern include intraluminal organising fibrosis in the distal airspaces, patchy distribution, preserved lung architecture, uniform temporal appearance and mild interstitial inflammation [31].

The available evidence is insufficient to confirm a causal relationship between HIV infection and organising pneumonia, particularly as HIV-infected patients are at risk of developing secondary organising pneumonia due to comorbidities or harmful exposures. In many small published series of patients with secondary organising pneumonia, HIV infection was not listed as one of the associated conditions, although patients were not systematically tested for HIV. Instead, some of the most common conditions associated with organising pneumonia included drugs (especially chemotherapeutic agents and amiodarone), radiation treatment and connective tissue disease [39–41].

The treatment for organising pneumonia classically consists of oral corticosteroids. In HIV-infected patients, one needs to weigh the degree of immunosuppression against the severity of the organising pneumonia before deciding on initiating therapy with oral corticosteroids. This is exemplified in a case report of a 14-year-old patient who received oral corticosteroid

for organising pneumonia and who died 2 months later after developing *Aspergillus fumigatus* lung infection [42]. However, there are a number of case reports showing improvement of symptoms and no major complications with corticosteroid therapy [8, 36]. In general, treatment with oral corticosteroid is favoured because organising pneumonia has been shown to have serious consequences if unrecognised [43].

Sarcoidosis

Sarcoidosis is a chronic granulomatous disease that can affect any organ system, although it more commonly affects the lungs, eyes and skin. Although it has been associated with a number of environmental factors, a definitive aetiology for sarcoidosis has not been identified [44]. It is well established that patients with sarcoidosis often develop alveolitis with a predominance of CD4⁺ T-cells in the lungs [45]. Because HIV fuses with CD4⁺ T-cells and leads to their depletion [46], some have argued that HIV infection might actually be associated with a lower risk of sarcoidosis development. In fact, only a few cases of concomitant HIV infection and sarcoidosis had been reported before the introduction of cART [47–51]. However, several case reports and series of concomitant HIV infection and sarcoidosis have been described in the cART era [7, 13, 52–54].

At presentation, symptoms are common and include dyspnoea, cough, and cervical or axillary adenopathy. Less commonly, patients present with uveitis, erythema nodosum, fever and skin nodules [13]. Usual radiographic manifestations include hilar or mediastinal adenopathy and parenchymal nodules [53]. In most reported cases, patients presented with radiographic stage I or II [13]. The bronchoalveolar lavage CD4⁺/CD8⁺ T-cell ratio is variable in the literature. Studies before the cART era showed a consistently low ratio [49, 51]. In patients who received ART, this ratio has been reported as being low, normal or high [7, 13, 54–56]. The diagnosis is established by the presence of granulomatous inflammation (typically characterised by noncaseating granulomas) in a tissue biopsy specimen after exclusion of infection by microorganisms such as spirochaetes, mycobacteria and fungi [53].

One important question related to the association of sarcoidosis and HIV is what comes first. Before the cART era, the diagnosis of sarcoidosis typically preceded the diagnosis of HIV. This is not the case in the cART era, where the diagnosis of sarcoidosis has generally been made after the initiation of treatment for HIV infection [7]. An analysis of pooled reported cases revealed that patients develop sarcoidosis approximately 14 months after cART onset. At the time of the diagnosis of sarcoidosis, patients have a peripheral CD4⁺ lymphocyte count that, on average, is slightly above 300 cells·μL⁻¹ and that has increased by a factor of 1.85 since ART onset [13]. In the setting of a CD4⁺ T-cell count less than 200 cells·μL⁻¹, the presence of granulomatous lung inflammation is more likely to be due a specific infectious aetiology rather than sarcoidosis [53].

An immune reconstitution syndrome has been implicated in the pathogenesis of sarcoidosis associated with HIV infection. As previously stated, the development of sarcoidosis typically coincides with an increase in peripheral CD4⁺ lymphocyte count brought about by cART. An immunohistochemistry analysis of a surgical specimen obtained from the lung of a patient with concomitant sarcoidosis and HIV infection revealed the presence of alveolitis mostly caused by CD4⁺ T-cells, which is in contrast to patients with LIP. Furthermore, the granulomas showed strong staining for IL-17, indicating a T-helper (Th)17 cell response, and IL-2, indicating a Th2 response. Both the granulomas and the alveolitis strongly stained for IL-1, indicating a Th1 cell response as well [52].

The absence of clinical trials makes it difficult to provide definitive recommendations regarding the treatment of sarcoidosis in the setting of HIV infection. Cases have been described where there was improvement in symptoms in both patients who received and who did not receive oral corticosteroid [7]. In the presence of symptoms, and particularly when there is evidence of immune system restoration, it seems reasonable to follow the same principles of sarcoidosis treatment as in non-HIV-infected individuals.

Drug-induced pulmonary toxicity

Patients with HIV infection are often prescribed a variety of drugs for the treatment of their disease or for prophylaxis against opportunistic infections. While these drugs are markedly beneficial and have changed the course of the disease, they also carry side-effects. Adverse events related to the respiratory tract are not among the most common in patients taking ART. Instead, they typically develop more systemic side-effects such as nausea, headache and diarrhoea [57]. However, drug-related lung toxicity has been described in the literature as outlined below.

Around 4% to 7% of patients taking the NRTI abacavir develop an idiosyncratic hypersensitivity reaction [14, 57]. Of these, 30% develop respiratory symptoms such as dyspnoea, cough or pharyngitis. In a cohort of 1803 patients with abacavir-related hypersensitivity reaction, a chest radiograph was obtained in 98 patients and was abnormal in 35% of them. The most common abnormalities were interstitial or bilateral infiltrates, followed by lobar infiltrates [14]. The abacavir-related hypersensitivity reaction can be prevented, to a large extent, by screening patients for the presence of the major histocompatibility complex class I allele HLA-B*5701 [58]. Carriers of this allele are at higher risk of hypersensitivity reaction and should not receive abacavir. Once a hypersensitivity reaction to abacavir is recognised, the drug should be immediately discontinued. The evidence for development of respiratory symptoms as a reaction to other ART medications is more anecdotal. For example, there is a case report of a hypersensitivity reaction to the NNRTI efavirenz. The clinical manifestations included fever, pruritic skin rash and fatigue. The chest radiograph revealed bilateral interstitial infiltrate and there was mild eosinophilia. The symptoms improved upon discontinuation of efavirenz [9].

Protease inhibitors may potentiate the risk of toxicity in patients receiving chemotherapy, particularly chemotherapeutic agents metabolised by cytochrome P450 3A4. This is the case of vinblastine, a drug used for the treatment of lymphoma. In a retrospective study of 32 HIV-infected patients who underwent chemotherapy for Hodgkin lymphoma, ritonavir was associated with a higher risk of neurological and haematological toxicity, while lopinavir was associated with a higher risk of grade 3–4 neurological toxicity. Three patients who received bleomycin developed lung toxicity [59]. Because of the small number of patients, it was not possible to draw a conclusion as to whether chemotherapeutic agents and protease inhibitors interact to cause lung toxicity, although it seems plausible that they do.

Indirect evidence that bleomycin by itself may potentiate the replication of HIV in the lungs and thus promote HIV-induced lung inflammation comes from a study of macaques infected with simian HIV. The interaction between bleomycin and simian HIV infection led to a marked infiltration of macrophages in the lung parenchyma of these macaques. The same did not occur with the bleomycin control (uninfected) macaque or with infected macaques not exposed to bleomycin [60].

There are also reports of lung toxicity related to drugs taken for prophylaxis of opportunistic infections in HIV-infected patients. For instance, hypersensitivity pneumonitis with concomitant skin rash, nonproductive cough, dyspnoea, hypoxaemia and peripheral eosinophilia has been described in a HIV-infected patient taking dapsone [61]. TMP-SMX has also been associated with a hypersensitivity reaction in a patient who developed fever, liver dysfunction, skin rash and an interstitial pneumonitis. Infection was ruled out as a cause of the pneumonitis and the patient improved upon discontinuation of the antimicrobial [62]. It has been suggested that HIV-infected patients are particularly susceptible to sulfamethoxazole toxicity. A potential mechanism for this increased susceptibility appears to be diminished glutathione concentrations in HIV-infected cells. The already diminished glutathione concentrations are further depleted by the sulfamethoxazole metabolite hydroxylamine [63]. The toxicity results in cell apoptosis, particularly of CD8⁺ cells [64].

Immune reconstitution inflammatory syndrome

In the setting of HIV infection, IRIS is defined as the development of a number of illnesses, including AIDS-defining conditions, autoimmune diseases and mucocutaneous disorders, after the initiation of cART [65]. Paradoxically, this syndrome occurs as the level of CD4⁺ T-cells increases, which indicates an important role of these reconstituted cells in the pathogenesis of the syndrome. Patients with IRIS have high levels of IFN- γ and IL-7, which reveals unbalanced homeostatic signals, and high proportion of effector memory CD4⁺ T-cells, an indication of high antigenic load [66].

A cohort study analysed 2610 HIV-infected patients who initiated cART or had their cART regimen changed, and demonstrated adequate response as determined by a decrease in viral load of at least 0.5 log₁₀ copies per mL or an increase in CD4⁺ cell count by 50% or more. Of these, 276 (10.6%) patients developed IRIS within 6 months of follow-up. The IRIS-defining conditions were predominantly infectious such as candidiasis, herpes simplex infection, mycobacterial disease, CMV infection and PCP [65]. Despite the overwhelming predominance of infectious conditions, autoimmune disorders can also occur. An example of a noninfectious condition is sarcoidosis, which was discussed previously in this chapter.

The clinical manifestations of IRIS vary and depend on the defining conditions, some of which are more prone to involve the respiratory tract. As an example, there are a few reports of paradoxical worsening of the respiratory status in patients treated for PCP who are started on cART. These patients developed acute respiratory failure and fever. The chest radiograph showed patchy alveolar opacities [67]. In other conditions affecting the respiratory tract, such as sarcoidosis, the presentation may not be as dramatic.

Because the development of IRIS is typically associated with the onset of cART in the setting of an opportunistic infection, there has been debate as to the ideal time for initiation of cART. A clinical trial that included 282 HIV-infected patients who presented with an opportunistic infection found that early initiation of cART, as opposed to late initiation, led to less AIDS progression/death. Early initiation of cART was defined as treatment within 14 days of starting treatment for the opportunistic infection [68]. If patients develop IRIS, the goal should be to recognise and adequately treat the opportunistic infection triggering it [69]. In most cases, cART should be continued and the best approach is close observation. For severe cases, corticosteroids can be used but this recommendation is based on case series [70].

Conclusion

The massive worldwide effort lead by researchers, clinicians and healthcare advocates targeting HIV in the late 1980s and early 1990s, and leading to the development of effective therapies, represents one of the most impressive examples of the dramatic advancements made in science and medicine in the past half century. These efforts turned what was once a deadly infectious disease into a chronic disorder. As the life expectancy of patients with HIV infection increases, chronic disorders have become more evident including cardiovascular, neurological, renal and lung disorders. Among the pulmonary disorders associated with HIV, the interstitial lung diseases stand out as a group of disorders whose incidence appears to be increasing and for which a clear understanding of their pathogenesis is lacking. HIV infection has been associated with interstitial pneumonias like LIP, NSIP and organising pneumonia, diseases that have been difficult to study in the past, leading to a paucity of data on how they relate to HIV infection. How HIV infection leads to these disorders; why these disorders manifest themselves in such distinct ways; and what host and viral factors trigger disease initiation, progression and, in some cases, remission, remain poorly understood. Research exploring viral–host interactions in the setting of HIV infection should be pursued, while carefully designed clinical trials should be conducted to determine the best treatment options, especially considering that the literature on treatment of these conditions is mainly anecdotal. Importantly, clinical, radiographic and pathological studies should be conducted to determine the true incidence, prevalence and natural history of interstitial lung disease in HIV-infected patients. Studies examining the mechanistic links between sarcoidosis and HIV and the mechanisms of drug-induced toxicity in the lung should also be considered. Considering that HIV has turned into a chronic disease, and that chronic lung disorders in this setting are increasing in frequency, efforts to bridge the gaps in knowledge in these areas should be encouraged.

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Pulmonary arterial hypertension

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PAH is found in approximately 0.5% of patients with HIV infection. The pathogenesis of PAH-HIV is not completely elucidated. It is widely believed that HIV plays an indirect role in the development of PAH-HIV as a result of production mediators, such as cytokines, growth factors or vasoconstrictors. The role of inflammatory mediators is supported by the presence of a marked inflammatory infiltrate in the pulmonary vessels of patients with PAH-HIV. The histopathological and clinical findings in PAH-HIV share many features with the idiopathic form of the disease. Until recently, PAH-HIV was associated with a particularly poor prognosis and patients with the disease tended to die from the effects of PAH rather than as a result of HIV infection. With the availability of ARTs given in combination with PAH-targeted therapies (prostanoids, endothelin receptor antagonists and phosphodiesterase type-5 inhibitors), the prognosis of the disease has markedly improved in recent years. Therefore, prompt diagnosis and effective treatment of PAH in HIV-infected patients remains essential. Taking into account currently available data and clinical experience, a treatment algorithm based on treatment guidelines for other forms of PAH is suggested.

HIV infection has been associated with both infectious and noninfectious complications. With the advent of better prophylaxis against infections, as well as longer survival secondary to cART, complications of HIV infection other than the typical problems of opportunistic infection and malignancy are emerging. The prolonged survival of this patient population has led to the recognition that HIV-infected individuals are more prone to develop PAH.

PAH results in a progressive increase in pulmonary vascular resistance (PVR) leading to increases in pulmonary pressures, right ventricular hypertrophy, right heart failure and, ultimately, death. In 1987, KIM and FACTOR [1] described, for the first time, the presence of PH and lesions of plexogenic pulmonary arteriopathy in a patient with AIDS. Since then, hundreds of cases of PAH associated with HIV infection (PAH-HIV) have been reported in the literature [2–8]. The clinical and histopathological findings in PAH-HIV share many features with the idiopathic form of the disease. This led to the inclusion of PAH-HIV as a distinct entity in group 1 (*i.e.* PAH group) of the clinical classification of PH, which has been recently updated (table 1) [9].

Until recently, PAH-HIV was associated with a particularly poor prognosis and patients with the disease tended to die from the effects of PAH rather than as a result of HIV infection [4, 6]. With the availability of ART given in combination with PAH-targeted therapies (prostanoids,

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Table 1. Updated clinical classification of PH

1. PAH

- 1.1. Idiopathic PAH
- 1.2. Heritable PAH
 - 1.2.1. *BMPR2* mutations
 - 1.2.2. Mutations of ALK-1, endoglin, SMAD9, CAV1, KCNK3
 - 1.2.3. Unknown
- 1.3. Drugs and toxins induced
- 1.4. Associated with:
 - 1.4.1. Connective tissue disease
 - 1.4.2. HIV infection
 - 1.4.3. Portal hypertension
 - 1.4.4. Congenital heart diseases
 - 1.4.5. Schistosomiasis
- 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
- 1''. Persistent PH of newborn

2. PH due to left heart disease

- 2.1. Left ventricular systolic dysfunction
- 2.2. Left ventricular diastolic dysfunction
- 2.3. Valvular diseases
- 2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to lung diseases and/or hypoxia

- 3.1. COPD
- 3.2. Interstitial lung disease
- 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4. Sleep disordered breathing
- 3.5. Alveolar hypoventilation disorders
- 3.6. Chronic exposure to high altitude
- 3.7. Developmental lung diseases

4. Chronic thromboembolic PH**5. PH with unclear multifactorial mechanisms**

- 5.1. Haematological disorders: chronic haemolytic anaemia and myeloproliferative disorders splenectomy
- 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis and vasculitis
- 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease and thyroid disorders
- 5.4. Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure and segmental PH

BMPR2: bone morphogenetic protein receptor type II; ALK-1: activin receptor-like kinase-1; CAV1: caveolin-1; KCNK3: potassium channel subfamily K member 3. Reproduced and modified from [9] with permission from the publisher.

endothelin receptor antagonists (ERAs) and phosphodiesterase type-5 (PDE-5) inhibitors), the prognosis of PAH-HIV has markedly improved in recent years [8, 10, 11]. Therefore, prompt diagnosis and effective treatment of PAH in HIV-infected patients remains essential. Taking into account currently available data and clinical experience, a treatment algorithm for PAH-HIV based on treatment guidelines for other forms of PAH has been suggested.

Epidemiology of PAH-HIV

Prevalence and incidence

Data from the French PAH patient registry, established in 2002, show that HIV infection represents ~7% of all cases of PAH diagnosed in 1 year [12]. In addition, ~4% of PAH

patients present with two co-existing risk factors, mainly HIV infection with portal hypertension [12]. If these patients are also taken into account, the total number of cases of PAH-HIV represents $\sim 10\%$ of all PAH cases [12]. Initial studies in the 1990s indicated that the prevalence of PAH in HIV-infected individuals was $\sim 0.5\%$ [2, 4]. In the current cART era, a prospective study conducted in 7648 consecutive HIV-positive adults in 14 HIV clinics in France found that this figure has not changed in recent years (0.46%, 95% CI 0.32–0.64%) [7]. Although the prevalence of PAH-HIV does not seem not to have changed, data from the Swiss HIV Cohort Study showed that the incidence of newly diagnosed cases has declined dramatically from 0.21% in 1995 to 0.03% in 2006 [10]. This decrease in incidence of PAH-HIV could be related to differences in population mix as a result of changes in modes of transmission, or may be associated with improvements in ART leading to higher CD4⁺ cell counts, better control of HIV replication and a decrease in immune activation (fig. 1) [10].

Demographics

PAH-HIV has been described in both HIV-1 and HIV-2 infection. Patients with PAH-HIV tend to present at a younger age than those with other forms of PAH and, unlike idiopathic PAH, which is more common in females than males (female/male ratio 1/1.7), males are more frequently affected by PAH-HIV (female/male ratio 1.2/1), possibly reflecting a link between the prevalent route of infection in PAH-HIV [3, 6, 12]. PAH-HIV arises regardless of the route of HIV infection, but is reported to be more frequent in intravenous drug users, with patients in this group representing 36–59% of cases of PAH-HIV in the French series [6, 8]. The role of *i.v.* drug use as a potential confounder has been ruled out, and it is now widely known that HIV infection is an independent risk factor for PAH [6]. There is no apparent correlation between the severity of PAH and the stage of HIV infection, the degree of immunodeficiency, or the CD4⁺ T-lymphocyte count [5, 6].

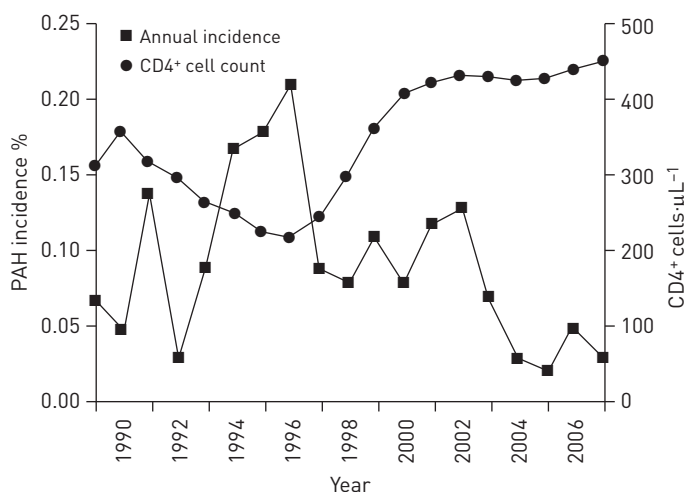


Figure 1. Annual incidence of PAH-HIV in the Swiss HIV Cohort Study compared with median CD4⁺ cell count of all Swiss HIV Cohort Study participants. Reproduced and modified from [10] with permission from the publisher.

Pathogenesis of PAH-HIV

Pathology

Pathological findings in PAH-HIV share broad similarities with the idiopathic and other forms of the disease, with medial hypertrophy resulting from pulmonary artery smooth muscle cell (PASMC) proliferation, endothelial cell proliferation and intimal fibrosis [13]. Plexiform lesions are found in ~80% of cases of PAH-HIV [5]. Pulmonary vein lesions (pulmonary veno-occlusive disease) are rarely observed in those patients [5]. Interestingly, there are also significant infiltrates of inflammatory cells (lymphocytes and macrophages) surrounding pulmonary vessels in patients with PAH-HIV, as has also been observed in PAH associated with connective tissue diseases [14].

Genetic predisposition

Several genetic mutations have been identified in patients with heritable and apparently idiopathic PAH [15]. The most frequent are the heterozygous germline mutations in bone morphogenetic protein type 2 receptor (*BMPR2*), a receptor for a member of the transforming growth factor- β superfamily. No *BMPR2* mutation has been ever identified in patients with PAH-HIV [6]. It might, however, be possible that *BMPR2* protein downregulation arises as a result of associated risk factors, such as viral infection, rather than a mutation. For example, the HIV-1 transcriptional transactivator (tat) protein represses *BMPR2* gene expression in human macrophages *in vitro*, interfering with the transcriptional regulation of bone morphogenetic protein and *BMPR2* [16].

Role of viral infection

There is currently no evidence to support a direct role of HIV in the pathogenesis of PAH-HIV and, although present in inflammatory cells in the lungs, the virus itself has never been found in the pulmonary vascular lesions seen in patients with PAH-HIV [17]. Therefore, it is widely believed that HIV plays an indirect role in the development of PAH-HIV as a result of production mediators such as cytokines, growth factors or vasoconstrictors, e.g. endothelin (ET)-1 [18]. The role of inflammatory mediators is supported by the presence of a marked inflammatory infiltrate in the pulmonary vessels of patients with PAH-HIV.

Endothelial cell dysfunction

It is widely believed that endothelial cell dysfunction plays a major role in the pathogenesis of PAH [13]. Endothelial cell dysfunction is characterised by the excessive production of ET-1 and the reduced production of nitric oxide and prostacyclin by the pulmonary vascular endothelium [19]. There are many more abnormalities that have been implicated in the pathogenesis of PAH, but these are the key mediators that have led to the development of novel therapeutic strategies and improvements in the management of the disease [19]. HIV viral antigens are present in the pulmonary endothelium and may stimulate apoptosis, cell growth and proliferation [18]. In particular, HIV-related proteins may affect ET-1 production by both endothelial and inflammatory cells [18]. The HIV-1 envelope glycoprotein 120, a viral protein involved in the binding and entry of HIV into macrophages, has been shown to target pulmonary artery endothelial cells, increase apoptosis and stimulate production and release of ET-1, as well as cytokines, including TNF from macrophages in a concentration-dependent manner [20]. The HIV-1 tat protein interacts with at least three different types of receptors present on the surface of endothelial

cells, which trigger various biological responses in the endothelium and may, therefore, be involved in the pathological processes that occur in PAH-HIV [18].

Inflammation

Inflammation is a common finding in PAH and is notably present in PAH-HIV [18]. Immunohistochemical techniques demonstrate the presence of activated inflammatory cells, including lymphocytes, macrophages, mast cells and immature dendritic cells in the pulmonary artery lesions of patients with PAH [18]. Chronic HIV infection induces an inflammatory state, persistent immune activation and dysregulation that could indirectly induce the release of proinflammatory cytokines (chemotactic cytokines, RANTES, fractalkine, *etc.*) and growth factors that may be involved in the pathogenesis of PAH [18].

Another important mediator is platelet-derived growth factor (PDGF). PDGF causes PASMC and fibroblast proliferation and migration, and thus may be involved in the remodelling of small pulmonary vessels. Both the protein and its messenger (m)RNA have been detected in the perivascular area of patients with PAH-HIV [17]. There is also increased expression of PDGF A-chain mRNA expression in patients with PAH compared with normal controls, and this increase has also been identified in patients with PAH-HIV [17].

Vascular endothelial growth factor-A, an angiogenic factor produced by T-cells infected with HIV, induces vascular permeability and endothelial cell proliferation and was, therefore, implicated in the development of vasculopathy in HIV-infected patients [16]. However, its role in the pathogenesis of PAH remains controversial [21].

HIV-1 Nef protein

The negative factor (*nef*) antigen, which is of major importance for the maintenance of HIV viral loads and for host cell signalling interactions, has been localised in pulmonary and vascular cell types in HIV-infected subjects. Human endothelial cells exposed *in vitro* to *nef* demonstrate increased apoptosis followed by proliferation [22, 23]. In a comparison of primates infected with a chimeric simian-HIV (SHIV) *nef* virion (containing the HIV *nef* gene in a simian immunodeficiency viruses (SIV) backbone) and those infected with the native SIV *nef* allele, pulmonary artery plexiform-like lesions were found exclusively in animals infected with SHIV human *nef* [22, 23]. In SHIV *nef*-infected animals, Nef antigen was localised to the endothelium of the lung vasculature. The pattern of Nef expression in patients with PAH-HIV was found to be similar to that seen in SHIV *nef*-infected primates, suggesting that *nef* may play a role in the development of PAH in HIV-infected subjects [22, 23]. Therefore, *nef* may induce apoptosis in endothelial cells; phagocytosis of such apoptotic cells may then initiate the release of growth factors and cytokines, which may lead to the emergence of apoptosis-resistant cells and uncontrolled endothelial proliferation [22, 23].

Human herpesvirus 8

Human herpesvirus (HHV)-8 has been implicated in the pathogenesis of idiopathic PAH based on the detection of latency-associated nuclear antigen 1 and the HHV-8a viral cyclin gene in lung tissue samples [24]. These findings are, however, considered controversial. Other studies have failed to demonstrate the presence of HHV-8 in lung tissue from patients with PAH [25], and have shown that plasma seropositivity does not differ between patients with idiopathic PAH and healthy controls. A specific role for the virus in PAH-HIV also seems unlikely, given that there does not appear to be increased serological evidence of HHV-8 infection in PAH in HIV-infected patients or in non-HIV-infected patients [26].

Clinical presentation and diagnosis of PAH-HIV

The major presenting symptoms of PAH in HIV-infected patients arise as a result of right ventricular dysfunction, and as such are similar to those seen in patients with idiopathic PAH. The primary symptoms of PAH are nonspecific and could relate to a number of underlying conditions, especially in HIV-infected individuals. The most common presenting features are progressive shortness of breath (85%), peripheral oedema (30%), cough (19%), fatigue (13%), syncope or near syncope (12%), and chest pain (7%) [5]. Physical examination most commonly reveals loud P2, right-sided S3 gallop, tricuspid regurgitation murmur, increased jugular venous pressure and peripheral oedema [5].

Although the presenting symptoms and clinical features of patients with PAH-HIV are similar to those reported for patients with idiopathic PAH, the time interval between the onset of symptoms and the establishment of diagnosis of PAH is shorter in patients with PAH-HIV (6 months *versus* 2.5 years, respectively). This may reflect the closer monitoring of HIV patients after the initial diagnosis of HIV infection [5, 6].

Chest radiographs in PAH-HIV often reveal right heart enlargement and prominence of the pulmonary arteries, with clear lung fields. An ECG may show nonspecific signs of right ventricular hypertrophy and, less commonly, right atrial abnormality, right axis deviation and sinus tachycardia [5]. Transthoracic echocardiography (TTE) may show a range of abnormalities, including right heart enlargement, tricuspid regurgitation and paradoxical septal motion abnormalities [27]. The presence of pericardial effusion is associated with a poor outcome. TTE may also be useful to detect left-sided heart disease, which is quite common in HIV-infected subjects.

Right heart catheterisation is the standard for diagnosing PAH, and evaluating haemodynamic status and response to treatment. PAH is defined by a mean pulmonary artery pressure (PAP) >25 mmHg with a mean pulmonary artery occlusion pressure <15 mmHg and PVR >3 Wood units [28].

To diagnose PH in a patient with HIV infection does not mean that this patient has PAH. Other forms of PH are much more common than PAH and physicians have to keep in mind the clinical classification of PH [9]. For example, tobacco smoking is more frequent in HIV-infected subjects than in the general population, and pulmonary emphysema is more frequent and severe in those patients [29]. As a result, PH related to COPD and emphysema has to be considered in such patients. At diagnosis of PH, pulmonary function tests and thoracic computed tomography (CT) are routinely performed. Other forms of PH include post-capillary PH (left-sided heart diseases) and chronic thromboembolic PH. In all cases, a complete work-up including TTE, ventilation/perfusion lung scan and contrast-enhanced CT has to be performed to make the right diagnosis.

Survival

The presence of PAH is an independent risk factor of mortality in patients with HIV infection, and historically the median survival of PAH-HIV patients was significantly lower than that of HIV patients without PAH [4]. In the 1990s, before the availability of cART, patients with PAH-HIV had poor outcomes, with 1-, 2- and 3-year survival rates of 73%, 60% and 47%, respectively [6]. Survival rate was especially low for patients in New York Heart Association (NYHA) functional classes III and IV, with a 3-year survival rate of only

28% [6]. In most cases of PAH-HIV, death has been reported to be causally related to PAH rather than to other complications of HIV infection [3], and complications associated with PAH were the direct cause of death in 72% of the PAH-HIV patients in the French cohort [6]. Recent data from 77 PAH-HIV patients followed at the French Reference Centre for PAH (Université Paris-Sud, Le Kremlin-Bicêtre, France) and all treated with cART, have shown that the overall survival has dramatically improved in recent years [8]. In that cohort, the overall survival rates were 88% and 72% at 1 and 3 years, respectively. On multivariate analysis, a cardiac index of $>2.8 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ and a CD4^{+} lymphocyte count of $>200 \text{ cells}\cdot\text{mL}^{-1}$ were independent predictors of survival [8].

To date, PAH-HIV is the type of PAH that is associated with the best survival rate amongst the PAH population (fig. 2) [11].

Treatment of PAH-HIV

Patients with PAH-HIV are usually excluded from the main randomised controlled trials (RCT) or when their inclusion was allowed, very few entered into the study. As a consequence, current recommendations for the treatment of PAH-HIV are largely based on data from patients with the idiopathic form of the disease or PAH associated with connective tissue disease. Therefore, caution is recommended if the current general guidelines for PAH therapy have to be extrapolated to other forms of PAH [30, 31]. Both the 2009 European treatment guidelines and the most recent recommendations from the 5th World Pulmonary Hypertension Symposium (Nice, France) in 2013 list PAH-HIV as a special condition and stress that evidence to support best management is lacking [30, 31]. Despite major progresses made in the care of chronic infection, noncurable infections including chronic, active, viral hepatitis and HIV are still absolute contraindications to lung transplantation.

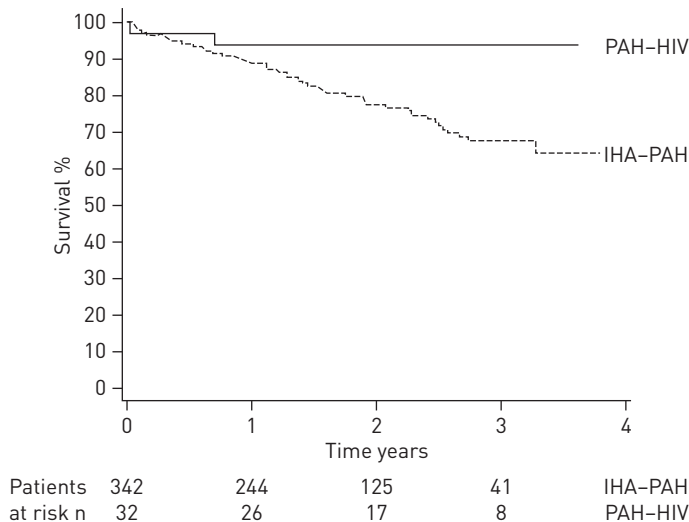


Figure 2. Kaplan-Meier survival curves in a cohort of newly diagnosed (*i.e.* incident) patients with idiopathic, heritable or anorexigen-associated (IHA)-PAH and PAH-HIV enrolled in the French Registry between 2006 and 2009. Data from [11].

Effects of ART on PAH-HIV

The effect of ART on PAH-HIV is controversial. Several studies have reported that ART can induce endothelial dysfunction in *in vitro* studies and animal models, resulting in increased ET-1 production and endothelial proliferation and, thus, potentially contributing to or exacerbating underlying PAH-HIV [32–34]. Treatment with cART (*i.e.* the combination of at least three antiretroviral drugs) was, however, shown to improve haemodynamics and survival in a retrospective analysis of 35 patients from the Swiss HIV Cohort Study [35]. In this group, right ventricular systolic pressure over right atrial pressure gradient increased by a median of 25 mmHg in nine patients who had not received ART, decreased by a median of 3 mmHg in 12 patients who had received NRTIs, and decreased by a median of 21 mmHg in 14 patients who had received cART ($p < 0.005$); although the effect of ART on this parameter was highly variable between patients [35]. In that small study, treatment with cART significantly decreased mortality as a result of PAH, as well as other causes, suggesting a beneficial effect of ART in patients with PAH-HIV [35]. In a study by BARBARO *et al.* [36], a significant improvement in exercise capacity as measured by the 6-min walking distance (6MWD) was seen in 18 patients with PAH-HIV after 12 weeks of therapy with cART alone (combination of two NRTI with either protease inhibitors, or NNRTI), but haemodynamic parameters were not improved. Similar results were found in a study by DEGANO *et al.* [8], which analysed 77 consecutive patients treated at the French Reference Centre for PAH between 2000 and 2008. All patients received cART and 50 patients received an additional PAH-specific therapy. cART and PAH-specific therapy led to improvements in 6MWD and haemodynamic parameters assessed by right heart catheterisation. In patients who did not receive PAH-specific therapy, 6MWD improved but haemodynamics did not change [8]. However, anecdotal reports described major improvement in haemodynamics after the introduction of cART in PAH-HIV patients refractory to a combination of PAH-specific therapies [37]. Furthermore, it has been shown in a recent experimental study that three first-generation HIV protease inhibitors (ritonavir, amprenavir and nelfinavir) partially protect against the development of hypoxia- or monocrotaline-induced PH in rats [38]. The three drugs also partially reversed established PH in monocrotaline-treated rats, an effect associated with diminished pulmonary vascular remodelling mainly due to inhibition of smooth muscle hyperplasia. One suggested mechanism of this growth-inhibiting effect is inhibition of the Akt signalling pathway, which is a downstream target of growth factors such as PDGF and serotonin [38].

Nonspecific therapies

Nonspecific therapies in PAH include those that are generally considered to be efficacious and beneficial, but for which there are few clinical data to support their use. Examples include supplemental oxygen, anticoagulants, oral vasodilators and digoxin [30, 31]. There are currently no RCTs on the use of those therapies in PAH-HIV. Therefore, in general, their use is based on experience from other forms of PAH. Treatment with oral anticoagulants is recommended as background therapy in patients with idiopathic PAH [30, 31], but their use in PAH-HIV needs to be considered in light of the risk of thrombocytopenia and associated liver disease frequently seen in these patients, and the potential for drug interactions, particularly with protease inhibitors [39]. There is little evidence to support their use in PAH-HIV, although *in situ* thrombosis is occasionally found in these patients [5]. In the absence of contraindications, however, treatment with anticoagulants may be given. Indication for calcium-channel blocker therapy in PAH is strictly restricted to patients exhibiting a positive response to acute vasodilator testing performed during the first haemodynamic assessment [40]. Acute pulmonary vasodilator response is rare in patients with PAH-HIV and, therefore, there is

almost no indication for long-term calcium antagonist treatment in such patients [41]. In addition, the use of calcium antagonists in PAH-HIV has been associated with side-effects and the potential for drug-drug interaction with ART [42].

PAH-targeted therapies

Intravenous epoprostenol and prostacyclin analogues

Epoprostenol is the synthetic form (sodium salt) of prostacyclin, and was first licensed by the US Food and Drug Administration (FDA) as a PAH treatment in 1995 based on improved functional class, exercise capacity, haemodynamics and survival compared with conventional therapy in a short-term RCT [43]. The structure of the epoprostenol molecule is unstable in solution and is prone to rapid degradation. Therefore, epoprostenol must be delivered by a continuous *i.v.* route through a permanent indwelling central venous catheter *via* a portable infusion pump system [43, 44]. Long-term treatment with *i.v.* epoprostenol has been shown to improve outcomes in patients with severe PAH [44]. To date, *i.v.* epoprostenol is the only agent recommended as a first-line treatment for patients with severe PAH categorised as NYHA functional class IV [30, 31]. Experience with *i.v.* epoprostenol therapy in PAH-HIV patients is limited [6, 45]. In a study by AGUILAR and FARBER [45], treatment with *i.v.* epoprostenol resulted in a significant improvement in functional class and haemodynamics in six patients with PAH-HIV; a significant decrease in mean PAP and PVR, and a significant increase in mean cardiac output was also seen. These improvements were maintained for at least 2 years. Similar results have been shown by NUNES *et al.* [6] in 12 patients with PAH-HIV treated with epoprostenol, leading to a marked improvement in exercise capacity, as measured by the 6MWD, and in pulmonary haemodynamics. These improvements were seen as early as 3 months and were sustained for a mean follow-up of 17 months [6]. Long-term survival was significantly better in patients treated with epoprostenol compared with patients on nonspecific therapy alone. The best outcomes were observed in patients receiving the combination of ART with epoprostenol [6]. Although these are encouraging results, continuous *i.v.* infusion is inconvenient and is associated with a risk of catheter-related infection. This risk is particularly important in HIV-positive patients who present with immunosuppression. A further consideration is the use of an *i.v.* preparation to treat *i.v.* drug users, especially given the high prevalence of such patients in the PAH-HIV population.

Subcutaneously administered or nebulised prostacyclin analogues may overcome the limitations of *i.v.* administration, but there are very few data on the use of these compounds in PAH-HIV. Treprostinil is a more chemically stable prostacyclin analogue with a longer plasma half-life than epoprostenol, allowing it to be administered intravenously, subcutaneously, orally or by inhalation. Continuous subcutaneous infusion of treprostinil was shown to improve exercise capacity in a 12-week, placebo-controlled RCT conducted in 470 PAH patients (PAH-HIV patients were excluded) [46]. The major limitation of this formulation is infusion site pain, which occurs in the vast majority of patients [46]. Approval of *s.c.* treprostinil was granted in 2002 in the USA and in 2005 in Europe. A small study of three patients with PAH-HIV in NYHA functional class IV treated with *s.c.* treprostinil showed an improvement in NYHA functional class and 6MWD within 12 weeks, which continued to improve over 1 year of treatment [47]. A decrease in systolic PAP (as estimated with TTE) was also reported in two patients [47]. There has been no experience with *i.v.*, inhaled or oral treprostinil in patients with PAH-HIV.

Iloprost is a stable prostacyclin analogue that is available for inhaled and *i.v.* administration. Due to its short half-life, inhaled iloprost needs to be administered six to nine times a day. In the AIR (Aerosolized Iloprost Randomized) study, a 12-week RCT, 17% of inhaled iloprost-treated

PAH patients reached the combined primary end-point of improvement in functional class, and a 10% increase in 6MWD was seen in the absence of clinical deterioration or death, compared with 5% of placebo-treated patients [48]. Following the AIR study, the European authorities and the US FDA granted regulatory approval for inhaled iloprost in 2003 and 2004, respectively. Experience with inhaled iloprost in PAH-HIV patients is limited. In a study by GHOFrani *et al.* [49], acute administration of inhaled iloprost reduced mean PAP and PVR, and improved cardiac index in eight patients with PAH-HIV. Long-term treatment with inhaled iloprost in four of the patients improved 6MWD and decreased PVR [49]. No major interactions with the ongoing ART were reported.

Oral PDE-5 inhibitors and guanylate cyclase activators

There are currently no RCTs of PDE-5 inhibitors (sildenafil and tadalafil) in PAH-HIV, and data for their possible effects come from case studies in which improvements in symptoms, functional class, exercise capacity and PAP have been reported [50, 51]. Sildenafil is largely metabolised by cytochrome P450 3A4 and there is a potential for drug interactions when co-administered with a number of antiretroviral drugs, particularly protease inhibitors. Interactions have been reported between sildenafil and indinavir [52], and saquinavir and ritonavir [53], resulting in major increases in sildenafil area under the curve and peak plasma concentration (C_{max}). However, recent data suggest that PAH-HIV patients on sildenafil and ritonavir-boosted protease inhibitors did not report any significant adverse reactions to sildenafil despite a sildenafil $C_{max} > 500 \text{ ng} \cdot \text{mL}^{-1}$ [54]. Therapeutic drug monitoring of sildenafil should be taken into consideration during treatment with ART in order to avoid over-dosage.

Since the therapeutic effect of PDE-5 inhibitors is dependent on baseline nitric oxide level (typically reduced in PAH), treatments that act directly on soluble guanylate cyclase (sGC) could potentially have a greater efficacy than PDE-5 inhibitors [55]. The sGC activator riociguat has been tested in a large RCT including 443 patients with PAH. Unfortunately, patients with PAH-HIV were excluded from study entry [55].

Oral ERAs

ET-1 is a potent pulmonary vasoconstrictor with a proliferative effect on PASMC. It interacts with two types of ET-1 receptors: ET-1 receptor isoform A (ETA), mainly localised on PASMCs; and ET receptor isoform B (ETB) mainly localised on the vascular endothelium and less so on PASMC [56]. Activation of the ETA isoform (and the ETB isoform on PASMC) induces vasoconstriction and proliferation of PASMC. The ETB receptors are principally involved in the clearance of ET-1 and may induce vasodilation *via* the release of nitric oxide and prostacyclin from the endothelial cells [56]. Currently, both selective and nonselective ERAs have been approved and are available for the treatment of PAH [56].

Bosentan is a dual ERA that has been approved since 2002 for the treatment of patients with PAH. Its efficacy has been confirmed in placebo-controlled RCTs enrolling several hundred patients with idiopathic PAH and PAH associated with connective tissue diseases and congenital heart defects [57–59]. Bosentan is the drug that has been investigated most in PAH-HIV. In an open-label uncontrolled study, BARBARO *et al.* [36] showed that treatment of 18 PAH-HIV patients with bosentan plus ART for 24 weeks resulted in significant improvements in 6MWD (15% increase) and in haemodynamic parameters compared with patients treated with ART alone. The prospective, open-label BREATHE (Bosentan Randomized Trial of Endothelin Antagonist Therapy)-4 study included 16 patients with PAH-HIV in NYHA functional class III–IV [60]. Of these, eight patients had AIDS, four had

asymptomatic HIV infection, four had co-infection with hepatitis C or B, and all but one were receiving ART. After 16 weeks of treatment, 6MWD improved by a mean of 91 m and functional class improved in all but three patients, with 13 patients being in NYHA functional class I or II [60]. Major improvements were observed in cardiac index, PVR and mean PAP. Patients also reported significant improvements in quality of life in six domains of the Short Form-36 questionnaire. Importantly, there was no clinically relevant impact of bosentan treatment on the efficacy of ART. CD4⁺ cell counts and viral loads remained stable and there were no significant changes in antiretroviral drug plasma concentrations over the study period. A retrospective study performed at the French Reference Centre for PAH showed a long-term beneficial effect of bosentan (mean treatment duration of 29 months) on functional class, exercise capacity and pulmonary haemodynamics without any change in the control of HIV infection [61]. Interestingly, resting pulmonary haemodynamics assessed by right heart catheterisation completely normalised in 10 out of the 59 patients in this series [61]. Since then, similar cases have been published, including two PAH-HIV patients with fully reversible PAH after a 4-year discontinuation of bosentan [62]. The long-term safety of bosentan in patients with PAH-HIV has been monitored as part of the Post-Marketing Surveillance database [63]. Between May 2002 and November 2004, 102 patients with PAH-HIV being treated with bosentan in daily medical practice were included in this database [63]. Long-term bosentan was well tolerated in this setting, and the incidence of liver enzymes elevation was similar in PAH-HIV and idiopathic PAH patients (8.8% *versus* 8.4%, respectively).

The data from these studies and the Post-Marketing Surveillance database suggest that bosentan has clinical and haemodynamic benefits in patients with PAH-HIV and is safe to use in conjunction with ART, with no adverse effects on the control of HIV infection. It should, however, be kept in mind that bosentan is an inducer of cytochrome P450 and, therefore, has the potential to interact with certain antiretroviral drugs. Although there is currently no evidence of clinically relevant interaction with these drugs, the usual parameters for monitoring the control of HIV infection should be checked regularly when combining bosentan and ART. In addition, several antiretroviral drugs are known to affect liver function and, therefore, monthly monitoring of liver function tests is important, particularly in patients with viral hepatitis B or C co-infection.

The selective ERA ambrisentan targets the ETA receptor. It has been shown to improve symptoms and exercise capacity, and delay time to clinical worsening in two RCTs [64]. Among the 393 PAH patients included in the studies, only 11 had PAH-HIV (2.8%) and no conclusion on the efficacy of ambrisentan in this subset of patients can be drawn, either from the RCTs [64] or the long-term study extension [65].

Macitentan is a new dual ERA with increased tissue penetration properties. The phase III SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) trial enrolled a total of 742 patients and is the largest prospective PAH study to date. Treatment with macitentan for ≥ 3.5 years, at a dose of 10 mg, decreased the risk of a first morbidity/mortality event by 45% *versus* placebo. Only 10 patients with PAH-HIV (1.4%) have been enrolled in the SERAPHIN study and no definite conclusion can be drawn in those patients.

Suggested treatment algorithm

Based on available data, the current recommended treatment algorithm for patients with PAH can be applied with some modifications to PAH-HIV (fig. 3). First, we strongly

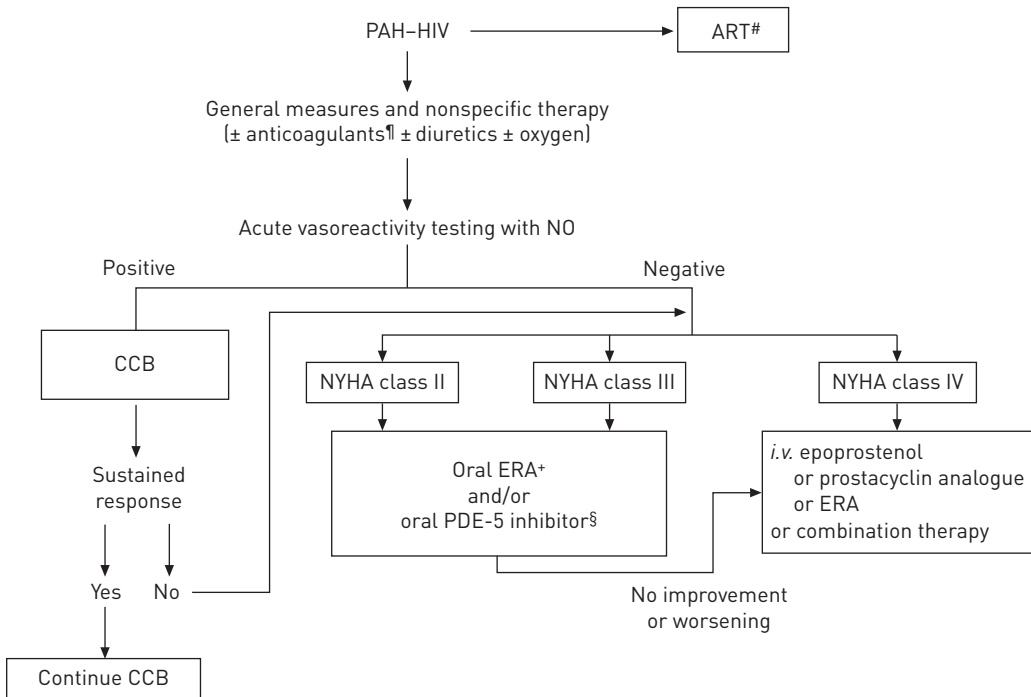


Figure 3. Proposed treatment algorithm for PAH-HIV. NO: nitric oxide; CCB: calcium channel blocker; NYHA: New York Heart Association; ERA: endothelin receptor antagonists; PDE-5: phosphodiesterase type-5. [†]: must be considered irrespective of the viral load or the CD4⁺ cell count; [‡]: before considering treatment with oral anticoagulant, drug-drug interactions with protease inhibitors must be taken in account; ⁺: contraindicated in the case of severe cirrhosis [Child-Pugh score C] or an increase in serum liver enzymes (alanine transaminase and aspartate aminotransferase) of more than three times the upper limit of normal; [§]: before considering treatment with PDE-5 inhibitor, drug-drug interactions with protease inhibitors must be taken into account; sildenafil and tadalafil are contraindicated with concomitant treatment with ritonavir. Reproduced and modified from [39, 66] with permission from the publishers.

recommend the use of cART as a background therapy in patients with PAH-HIV, even if its effect on the pulmonary vasculature remains to be confirmed. cART must be given in those patients irrespective of the viral load and the CD4⁺ cell count. Symptomatic treatments are indicated if needed (*e.g.* diuretics for fluid retention, oxygen for severe hypoxia, *etc.*) Careful attention must be paid to anticoagulation. Before considering treatment with oral anticoagulant, the presence of coagulation disorders (thrombocytopenia) and the possible drug-drug interaction with protease inhibitors have to be taken into consideration. Given the rarity of vasodilator response in patients with PAH-HIV and the potential for side-effects and drug-drug interaction with ART, there is very little indication for calcium antagonists. The majority of evidence regarding the use of disease-specific therapies in PAH-HIV comes from studies using the dual ERA bosentan. Clinical studies and “real world” safety data suggest that bosentan is the first-line therapy of choice for patients with PAH-HIV in NYHA functional class II–III. For patients with more severe PAH (NYHA functional class IV), epoprostenol should currently be considered to be first-line therapy, although bosentan may also be effective in this population. There are very few data to support the usefulness of other ERAs, PDE-5 inhibitors and prostacyclin analogues in PAH-HIV. In addition, there is the potential for drug-drug interactions between PAH therapies and some ART, in particular protease inhibitors, which may require monitoring and dose adjustments, or may contraindicate some combinations.

Conclusion

In conclusion, PAH is a rare but life-threatening complication of HIV infection. There is no correlation between the route of HIV transmission, the stage of HIV infection, the degree of immunosuppression and the prevalence or severity of PAH. Even if the pathogenesis of PAH-HIV is incompletely understood, HIV would play an indirect role by stimulating production and release of inflammatory mediators and growth factors in the pulmonary circulation. The role of ART in PAH-HIV is still controversial, but some experimental studies and clinical findings are in favour of its use in this subset of patients, irrespective of its indication for the HIV infection (viral load and CD4⁺ cell count). On the basis of limited data, patients with PAH-HIV appear to respond well to treatment with epoprostenol, although continuous *i.v.* infusion is associated with a range of potential side-effects and complications. Treatment with the oral dual ERA bosentan has been shown to benefit patients with PAH-HIV without adversely affecting the control of HIV infection, and without significant interaction with ART. However, careful monitoring of patients is recommended because of the potential for drug-drug interactions with ART and possible effects on the liver. Generalisation of access to care and availability of ART in combination with PAH-targeted therapies have led to a major improvement in the prognosis of patients with PAH-HIV.

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Bronchiectasis

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The immune defects associated with HIV infection increase susceptibility to lower respiratory infections and may predispose to the development of bronchiectasis. Bronchiectasis should be considered among the pulmonary manifestations of HIV infection, although the true incidence of bronchiectasis in this population remains to be established. It is especially important to consider the disease in patients with recurrent respiratory infections, a history of mycobacterial disease, or persistent or intermittent productive cough; diagnosis should be made using high-resolution computed tomography. An HIV test should be included as part of the diagnostic work-up both in patients with risk factors for HIV and in those from areas with significant levels of HIV infection. Early diagnosis and assessment in a specialist respiratory medicine unit, particularly in the event of chronic bronchial infection or recurrent exacerbations, may reduce the progression of bronchiectasis. It is probable that bronchiectasis in LIP is a different entity requiring different treatment and management.

HIV infection might be associated with LIP and recurrent infections. It is possible that both disorders are associated with different types of bronchiectasis. Although they have been described together, their pathogenesis, clinical and treatment implications may be completely different [1–4]. Bronchiectasis caused by damage to the bronchi wall as a result of inflammation secondary to infections will be the main subject of this chapter.

The immune defects associated with HIV infection increase susceptibility to lower respiratory infections and may predispose to the development of bronchiectasis. Conventional and opportunistic pulmonary pathogens, including mycobacteria species [5] and *Streptococcus pneumoniae*, are the main causes of infection in these patients. Approximately 13% of TB cases occur in HIV-infected individuals [6]. Both pneumonia prophylaxis and ART have led to changes in the epidemiology of HIV-associated lung diseases and led to improvements in the longevity of those infected with HIV. However, lung infections are still a major problem in settings with limited resources and in patients with poor HIV control; even in well-controlled HIV-infected patients, there continues to be an increased risk of pulmonary infection [7]. Other mechanisms have been suggested as being implicated in the development of bronchiectasis in HIV-infected patients; these include the direct effects of HIV infection on T-cell-dependent immunity and local macrophage- and monocyte-dependent pulmonary immunity, the secondary effects on humoral responses, and the association with COPD [8].

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Despite the fact that HIV infection is included in the list of causes of bronchiectasis [3, 4], little research has been performed in this area. This may be due in part to insufficient attention to bronchiectatic symptoms, as these patients are not usually seen by pulmonologists, so it is likely that few high-resolution scans looking for bronchiectasis are ordered.

Four studies of bronchiectasis with a comprehensive investigations of the aetiologies included HIV screening; however, this was restricted to patients with risk factors or other features suggesting the diagnosis [9–12]. The results of these studies show that very few HIV diagnoses were made. In a retrospective study of a paediatric population, LI *et al.* [11] found the highest number, a total of five cases (3.7% of all the patients studied). The study by PASTEUR *et al.* [10], performed in a northern European population, reported that no patient was known to be HIV positive (table 1). Bronchiectasis in these patients should be managed following the current guidelines [3, 4].

Bronchiectasis in adult patients with HIV infection

Bronchiectasis was first recognised as a complication of HIV disease in five patients in 1992 by HOLMES *et al.* [13]; few cases have been reported in other studies [2, 14, 15]. MCGUINNESS *et al.* [2] reported eight cases that were associated with episodes of pyogenic infection, four of which also had documented opportunistic infections. VERGHESE *et al.* [15] described three patients with bronchiectasis in the lower lobes and recurrent respiratory infections; *Staphylococcus aureus*, *Haemophilus influenzae*, *Burkholderia cepacia* and *S. pneumoniae* were isolated from sputum cultures.

The first study to investigate the prevalence of bronchiectasis in an HIV population was published in 1997 by KING *et al.* [16]. 50 HIV-positive adults without a history of AIDS-related pulmonary complications and 11 HIV-negative control subjects were included. High-resolution computed tomography (HRCT), bronchoalveolar lavage (BAL) and pulmonary function tests were performed. None of the HIV-negative subjects had bronchial dilatation; however, 36% of the subjects with HIV infection had mild bronchial dilatation on computed tomography (CT). None had a history of pneumonia, TB or asthma that may have predisposed them to bronchiectasis, and only seven had symptoms that fitted with bronchiectasis. The time that elapsed from the date of diagnosis of HIV infection to the date of CT was significantly greater for subjects with bronchial dilatation. The presence of bronchial dilatation significantly correlated with increased levels of neutrophils in BAL. No differences in smoking history, infection history or degree of immunosuppression were found between patients with and without bronchial dilatation, although there was a high proportion

Table 1. Studies of bronchiectasis patients that included HIV screening

First author [ref.]	Subjects n	Mean ± sd age years	Population	Males n	HIV infection n (%)	Unknown aetiology n (%)
NIKOLAIZIK [9]	41	Not reported	UK	Not reported	1 (2.4)	15 (36.6)
PASTEUR [10]	150	52.7 ± 15.2	Northern European	56	0 (0)	80 (53)
LI [11]	136	12.1	UK	65	5 (3.7)	35 (26)
McSHANE [12]	106	61.4 ± 17.7	USA	24	1 (0.9)	7 (6.6)

of smokers (62% of HIV-positive patients and 45% of HIV-negative patients). KING *et al.* [16] hypothesised that there were several possible causes of bronchial dilatation in these patients, such as bronchiolitis obliterans (although none had evidence of airflow obstruction), LIP or the effect of elevated levels of neutrophils in the airways.

In 1998, BARD *et al.* [17] described three HIV-seropositive adults with bilateral bronchiectasis predominantly in the lower lobes. These patients suffered from chronic cough and sputum, recurrent bronchitis and rapid worsening of dyspnoea and airway obstruction. All were smokers and other causes of bronchiectasis, such as childhood infection, α_1 -antitrypsin deficiency, allergic bronchopulmonary aspergillosis, hypogammaglobulinaemia and mycobacterial or fungus infection, were ruled out. BAL showed an increased number of neutrophils in two patients. *H. influenzae* was isolated from the bronchial brush in one patient, and *S. pneumoniae* and *Pseudomonas aeruginosa* were isolated in another. In the third patient, *P. aeruginosa* was isolated from a sputum culture.

In a recent cross-sectional study of 243 HIV-infected smokers with a mean age of 44.3 years, RAHMANIAN *et al.* [18] reported bronchial dilatation in the HRCT of 22.2% of men and 16.6% of women.

Pneumocystis lung colonisation detected by PCR assay is common in HIV-infected patients and has been implicated in the pathogenesis of HIV-associated COPD. The clinical significance is unknown but a role in chronic inflammation and progression of obstructive airway disease has been suggested [19]. Bronchiectasis does not seem to have been investigated in these patients.

Bronchiectasis in children with HIV infection

Five studies have been performed in paediatric populations.

A retrospective review by SHEIKH *et al.* [20] included 164 children with HIV infection and respiratory problems. Patient history was considered significant if intermittent cough and sputum production were present, and inspiratory crackles were noted on physical examination. The diagnosis of bronchiectasis was made using a chest radiograph in 26 of the 164 (15.8%) patients; however, the diagnosis was only confirmed by CT in 10 of the 26 patients and by autopsy in two patients, reducing confirmed diagnoses to 7.3% of the patients. The diagnosis of bronchiectasis *via* chest radiograph was based on the presence of an increase of pulmonary markings, loss of lung volume, bronchial wall thickening with dilatation, honey combing and cystic spaces; diagnosis *via* CT was based on air fluid levels in distorted bronchi, clusters of cysts, distended bronchi in the lung periphery and bronchial wall thickening. In cases in which CT or autopsy were performed, the diagnosis of LIP was made in eight out of 12 patients, none of whom had respiratory complications, but bacteria was recovered by BAL in four out of five cases in which BAL culture was performed (*Pseudomonas* and *S. aureus* in three cases, and *Streptococcus viridans* and *Corynebacterium* in one). All four patients without LIP had respiratory complications: recurrent pneumonia in two of the patients, non-resolving pneumonia in one and pulmonary TB in one. BAL culture was only performed in the patient with non-resolving pneumonia who was negative for and in the patient with TB who was positive for *Pneumocystis* and *Mycobacterium tuberculosis*.

A 2-year prospective longitudinal study, conducted between 1995 and 1997, in 194 children with persistent lung disease attending a respiratory clinic in South Africa, was performed by

JEENA *et al.* [21]. Persistent lung disease was defined as lasting clinical and radiological findings after at least 1 month of initial treatment. HIV testing and HRCT were performed in all patients. 71% of the patients were HIV infected; of these, 14% had persistent pneumonia or bronchiectasis. 27% of the patients were not HIV infected and of those, 23% had bronchiectasis.

In 2007, BERMAN *et al.* [22] performed a retrospective case–controlled study in order to define the possible risk factors that could lead to the development of bronchiectasis in patients with HIV-1 infection. 19 HIV-1-infected children who developed bronchiectasis while being cared for between January 1982 and September 2000 were matched with 57 control HIV-1-infected children without bronchiectasis. The mean age at diagnosis of bronchiectasis was 93 months (range 41–175 months). All of the children who developed bronchiectasis and 58% of the control group had an AIDS-defining illness. Only six of the 19 patients had sputum culture results in their medical record: *P. aeruginosa* in three patients; *P. aeruginosa* (mucoid phenotype) *S. pneumoniae* and *H. influenzae* in one patient; *S. pneumoniae* in one patient; and *Mycobacterium fortuitum*, *S. pneumoniae* and *H. influenzae* in one patient. Seven patients had LIP. 89% of patients who developed bronchiectasis had recurrent pneumonia that preceded the diagnosis of bronchiectasis; this was significantly higher than in patients without bronchiectasis. In addition to the fact that it was retrospective, an important limitation of the study is that the diagnosis of bronchiectasis was based on written documentation of chest radiograph and/or histological evidence in the medical record, and CT was only performed in five patients (the diagnosis was made *via* chest radiograph in 12 patients, CT in five and histopathology in two). Another limitation pointed out by the authors themselves is that the diagnosis of previous pneumonia was not always confirmed by examination of chest radiographs. The study suggested that recurrent pneumonia, profound immunosuppression and a previous diagnosis of LIP were potential risk factors for the development of bronchiectasis in HIV-1-infected children. Recurrent pneumonia or recurrent infections as a consequence of immunosuppression seem to be the most likely factors for the development of bronchiectasis. This is consistent with cystic fibrosis studies in which the development of bronchiectasis may be seen to occur earlier, and free neutrophil elastase activity in BAL fluid and lung infection were risk factors for both the development and progression of bronchiectasis [23, 24].

A cohort of 35 HIV-infected children assessed in a clinic in South Africa during 2009 was studied by MASEKELA *et al.* [25] in 2011. The children had symptoms of bronchiectasis confirmed radiologically. It is not clear whether HRCT was performed. It is likely that most of these children had vertically transmitted HIV and, hence, a delayed diagnosis of HIV, as most were diagnosed after reaching 6 years of age. The study was carried out in a high TB-burden area and 75% had previously received at least one course of anti-TB treatment. A complete assessment was made with induced sputum cultures, lung function tests, sputum and systemic inflammatory markers, and HIV viral load. All but one received ART at enrolment. The median FEV₁ was 53%. Two patients had severe bilateral lung disease with respiratory insufficiency; these patients died at follow-up. There were no differences in FEV₁, anthropometric parameters, months on ART, IL-4, IL-8, IFN- γ or immunoglobulin (Ig)G between patients with viral loads <25 copies·mL⁻¹ and with >25 copies·mL⁻¹. At presentation, 42.8% of the subjects had a positive sputum culture for a bacterial pathogen, the most common being *H. influenzae* and *H. parainfluenzae* (49% of all cultures). Less common were *P. aeruginosa* (2%) and *S. aureus* (1%). Two subjects had non-tuberculous mycobacteria (*M. fortuitum* and *Mycobacterium avium intracellulare*). No differences in FEV₁ were observed between patients with positive and negative sputum culture at enrolment.

Serum IgG levels and sputum IL-8 were elevated, as is the case in other patients with bronchiectasis [26–28].

In Zimbabwe, FERRAND *et al.* [29] studied 100 older children in stable state with vertically acquired HIV infection in whom clinically chronic lung disease was suspected. Suspected chronic lung disease included two or more of the following features: chronic cough, recurrent respiratory tract infections, moderate-to-severe limitation in physical activity caused by breathlessness, existing diagnosis and/or signs of cor pulmonale, and hypoxia at rest or desaturation on exercise. Sputum culture was performed in 54 patients and several bacteria were isolated (*H. influenzae* in six patients, *S. aureus* in five, *Moraxella catarrhalis* in five, *P. aeruginosa* in three, *S. pneumoniae* in two, *Klebsiella pneumoniae* in one, and *Listeria monocytogenes* in one). *M. tuberculosis* was confirmed in eight patients. HRCT was performed in 56 patients and bronchiectasis was found in 24. Decreased attenuation consistent with small airway disease was the most common and most extensive HRCT abnormality observed, although only a few HRCT images were obtained in the expiratory phase. The authors suggested that recurrent bacteria and viral respiratory tract infections, together with HIV-induced impairment of innate immune response, may predispose to chronic lower respiratory tract inflammation in these patients. Furthermore, these patients may be predisposed to an inflammatory obliterative bronchiolitis by HIV itself, and together these may facilitate airway remodelling and development of bronchiectasis. Malnutrition and aspiration pneumonia due to gastro-oesophageal reflux disease, oesophagitis by *Candida albicans*, or swallowing dysfunction, have also been suggested as other possible risk factors for the development of bronchiectasis in these patients [30].

Conclusion

Bronchiectasis should be considered among the pulmonary manifestations of HIV, even though the true incidence of bronchiectasis in this population remains to be established. Bronchiectasis should particularly be investigated in patients with recurrent respiratory infections, history of mycobacterial disease, or persistent or intermittent productive cough. Diagnosis should be made using HRCT. An HIV test should be included as part of the diagnostic work-up both in patients with risk factors for HIV and in those from areas with significant levels of HIV infection. Early diagnosis and assessment in a specialist respiratory medicine unit, at least in the case of chronic bronchial infection or recurrent exacerbations [3], may reduce the progression of bronchiectasis. It is probable that bronchiectasis in LIP is a different entity requiring different treatment and management.

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Immune reconstitution inflammatory syndrome

David M. Murdoch

IRIS is an increasingly recognised complication of ART initiation, particularly in HIV patients co-infected with other infectious pathologies. The syndrome is characterised by a clinical picture of an unexpected and often exuberant inflammatory response following ART. Clinically, the syndrome is most commonly classified as an unmasking or paradoxical form. Although these definitions have increased understanding of its pathogenesis and risk factors, the clinical diagnosis of IRIS remains challenging due to its heterogeneous infectious and noninfectious aetiologies, and spectrum of clinical severity. Although IRIS imparts a significant morbidity, including increased hospitalisation rates and diagnostic procedures, direct IRIS-attributable mortality is low. The mainstay of treatment is continuation of ART and, in severe or life-threatening presentations, the administration of nonsteroidal anti-inflammatory drugs and/or systemic corticosteroids. Cessation of ART may also be necessary if inflammation is severe and life threatening, or if the differential includes drug toxicity.

Following the development of successful ART for the treatment of HIV infection, an unexpected consequence has been IRIS. Also termed “immune restoration disease”, the syndrome is characterised by unexpected, exuberant symptoms following the introduction of ART. Although typically associated with more recent ART regimens, following the introduction of azidothymidine monotherapy in the early 1990s, treating clinicians noted successful restoration of host immune responses to infectious pathogens. Early IRIS pathogens included atypical mycobacteria with immune restoration documented as restored cutaneous reactivity to a tuberculin (purified protein derivative) antigen [1]. It was not until the introduction of protease inhibitors and the expansion of ART regimens to increasing numbers of HIV/AIDS patients in the late 1990s that the syndrome became more clinically frequent and obvious. An early prospective IRIS study included HIV/TB co-infected patients initiating ART in the USA [2]. Paradoxical symptoms, including fever and worsening pulmonary infiltrates, lymphadenopathy and effusions, were documented in 36% of TB-infected patients initiating ART. Strong cutaneous purified protein derivative conversions were again noted after ART initiation, raising valid public health concerns of HIV/TB co-infection. Subsequent retrospective studies and case reports of various infectious and noninfectious presentations of IRIS added to our understanding of the syndrome [3–11]. While limited by their retrospective nature, consistent and increasing reports of IRIS, particularly involving mycobacteria with pulmonary manifestations, drew early concern for the potential impact of IRIS in sub-Saharan Africa where the burden of TB and other

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opportunistic infections is high. The widespread rollout of ART in more resource-limited countries in the early 2000s presented the opportunity to study its potential impact. The first prospective IRIS study in sub-Saharan Africa revealed that 10.4% of patients initiating ART experienced some form of IRIS, with TB-associated IRIS constituting nearly half of the cases [12]. Shortly thereafter, case definitions for TB-IRIS were developed to guide the clinical diagnosis of IRIS in resource-limited settings and pave the way for more standardised clinical definitions of the syndrome and investigation of its pathogenesis [13].

Infectious and noninfectious manifestations of IRIS continue to populate the literature, reinforcing the systemic immunological pathogenesis of the disease. Its diagnosis remains challenging even for the most astute clinicians. For these reasons and given the respiratory focus of this *Monograph*, this chapter will highlight the pulmonary manifestations of IRIS with emphasis on pulmonary TB-IRIS, but will also draw on the nonpulmonary and noninfectious IRIS literature where necessary. For the interested clinician, other comprehensive reviews of IRIS are available [14, 15]. Other less common but important pulmonary manifestations of IRIS will also be discussed.

Immunopathogenesis

The immunopathogenesis of IRIS is largely unknown, although several hypotheses exist. Underlying most of these is the theory that restored cellular immunity to specific infectious or noninfectious antigens precipitates an exaggerated inflammatory response [15–17]. Early postulations proposed this being driven by a rapid redistribution of memory T-cells following ART therapy, with early pathological investigations lending support for this mechanism [10, 18, 19]. Ultimately, a murine model for *Mycobacterium avium* complex (MAC)-associated IRIS was developed by BARBER *et al.* [20] to further elucidate the immunopathogenesis of IRIS. In this model, MAC-infected T-cell-deficient mice were augmented with CD4⁺ T-cells. This action precipitated disease in mice with high mortality and marked inflammation characterised by donor CD4⁺ T-cell production of IFN- γ . Contrary to the prevailing thought, the disease was not dependent on baseline lymphopenia but associated with impaired T-cell proliferation and function. Such impaired IFN- γ production to mycobacterial antigens has also been documented in ART-naïve subjects initiating therapy without IRIS. While demonstrating significant increases in IFN- γ production, this increase peaked at a delayed 8 months following ART initiation and did not reach IFN- γ production levels of the HIV-negative controls [21]. BARBER *et al.* [20] conclude that IRIS may be driven by heightened antigen-specific CD4⁺ sensitivity to an antigen load, rather than rapid expansion or redistribution of an existing memory T-cell pool. In humans, this mechanism is supported by the observation of a sharp amplification of purified protein derivative-specific IFN- γ T-cells with T-helper (Th)1 cytokine production (IL-2, IL-10 and IFN- γ). No increase in Th2 cytokines occurred, and these results were again independent of CD4⁺ cell counts, as well as HIV RNA levels and the timing of ART initiation [22].

Further human IRIS immunopathogenesis studies are often limited given the inherent difficulties of immunological studies and the heterogeneity of IRIS presentations. Small case series and case-control studies have largely focused on differences in cytokine profiles due to a prevailing pro-inflammatory balance hypothesis and assay accessibility. Although reported cytokine associations vary, IL-6, IFN- γ and Th1-dominant cytokines persist throughout the literature [22–26]. In particular and not surprisingly, increases in IFN- γ are most often associated with IRIS [22, 24, 27]. Cellular-based immunology studies are even more difficult to conduct, with various studies suggesting a variety of cell types and generating a disparate

set of immunological mechanisms and hypotheses. Regulatory T-cells (Tregs) have generated interest due to their suppressive capacity and the proposed immunological imbalance in IRIS. While some studies report no differences in FoxP3⁺ Tregs, others have demonstrated increases in Tregs but with impaired suppressive function [23, 28]. Other proposed cellular mechanisms include the presence of activated antigen-specific effector memory CD4⁺ T-cells and $\gamma\delta$ T-cells in TB-IRIS patients [29]. $\gamma\delta$ T-cells play a role in host defence against bacterial ligands, including TB. Finally, CD8 T-cell activation (as defined by CD38⁺ HLA-DR⁺ cells) has also been associated with IRIS [30]; however, whether this phenotype is causative or as a consequence of IRIS is unknown but probably the former given the low specificity of such activation markers. All of these small studies contribute to our understanding of the immunopathogenesis of the syndrome. However, even in the most controlled study settings the complexity of any immune response is often difficult to elucidate. The heterogeneity of IRIS and lack of relevant animal models make the study of IRIS even more difficult, as it is likely that IRIS is a result of distinct but related immunological mechanisms [31].

***Mycobacterium tuberculosis* IRIS**

Definitions and epidemiology

IRIS is generally described as an abrupt onset of clinical symptoms characterised by inflammation and clinical deterioration following the initiation of ART. It is associated with a reconstitution of immune responses to either infectious or noninfectious antigens, with the latter including self or tumour-associated antigens [15]. The early observation that pulmonary TB patients on TB treatment developed worsening TB symptoms following ART initiation led to the term “paradoxical” IRIS [2]. However, the diagnosis of TB associated with exuberant inflammation following ART initiation in patients without TB prior to ART initiation led to the description of an “unmasking” form of the syndrome. Various case definitions existed, prompting the formation of more unified case definitions in 2008 (table 1) [13, 33–35]. Definitions for paradoxical TB-IRIS are often more straightforward given the pre-ART diagnosis of TB and worsening clinical symptoms that are frequently dramatic, such as worsening lymphadenopathy, fever, acute respiratory failure and acute respiratory distress syndrome (fig. 1) [36–38]. However, even with paradoxical pulmonary TB-IRIS, discerning whether a worsening infiltrate or effusion in the absence of dramatic symptoms is due to IRIS or is within the expected clinical course for pulmonary TB infection is often challenging.

Even more clinically challenging is the diagnosis of unmasking TB-IRIS, which is complicated further by the requirement that the patient is not receiving TB treatment at the time of ART initiation [13]. Variation in constitutional TB infection symptoms (cough, weight loss, *etc.*), site-specific TB screening practices, clinical experience and TB diagnostic capabilities probably result in substantial variation in the pre-ART diagnosis of TB. While unmasking TB-IRIS is defined as a “heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component” [13], the determination of whether a presentation of post-ART TB is abnormally exuberant or within that expected for TB infection can be difficult and clinically subjective. These case definition caveats should be considered when diagnosing pulmonary TB-IRIS, particularly in research settings attempting to determine IRIS incidence and in cases where decisions to initiate or discontinue ART are being considered.

Despite the clinical challenge of the diagnosis of TB–IRIS, pulmonary manifestations are relatively frequent compared with other IRIS aetiologies, and more standardised TB–IRIS definitions, such as the International Network for the Study of HIV-associated IRIS criteria, have resulted in accurate estimates of its incidence among HIV/TB co-infected patients initiating ART in large clinical trials. Prior to prospective trials, retrospective cohort studies estimated that 8–43% of TB-infected patients initiating ART experience paradoxical TB–IRIS [2, 3, 6, 39–43]. An early decision analysis of the timing of ART in HIV/TB co-infected patients reported that the highest rates of IRIS occurred in those initiated on ART within 2 months of TB therapy [44]. These considerable incidence estimates, the temporal association of IRIS and ART initiation, and concerns over its potential mortality and

Table 1. Case definition for paradoxical TB–IRIS

Antecedent requirements

Both of the following requirements must be met:

Diagnosis of TB: the TB diagnosis was made before starting ART and this should fulfil WHO criteria for diagnosis of smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB [32]

Initial response to TB treatment: the patient's condition should have stabilised or improved on appropriate TB treatment before ART initiation, *e.g.* cessation of night sweats, fevers, cough and weight loss (note: this does not apply to patients starting ART within 2 weeks of starting TB treatment since insufficient time may have elapsed for a clinical response to be reported)

Clinical criteria

The onset of TB–IRIS manifestations should be within 3 months of ART initiation, re-initiation or regimen change because of treatment failure

Of the following, at least one major criterion or two minor clinical criterion are required:

Major criteria:

New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement, *e.g.* tuberculous arthritis

New or worsening radiological features of TB (found by chest radiography, abdominal ultrasonography, CT or MRI)

New or worsening CNS TB (meningitis or focal neurological deficit, *e.g.* caused by tuberculoma)

New or worsening serositis (pleural effusion, ascites or pericardial effusion)

Minor criteria:

New or worsening constitutional symptoms such as fever, night sweats or weight loss

New or worsening respiratory symptoms such as cough, dyspnoea or stridor

New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly or abdominal adenopathy

Alternative explanations for clinical deterioration must be excluded if possible[#]

Failure of TB treatment because of TB drug resistance

Poor adherence to TB treatment

Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary TB and extrapulmonary TB where the initial TB diagnosis has not been microbiologically confirmed)

Drug toxicity or reaction

WHO: World Health Organization; CT: computed tomography; MRI: magnetic resonance imaging; CNS: central nervous system. [#]: it might be difficult or impossible in resource-poor settings to confirm TB drug resistance and to exclude certain other infections or neoplasia. Cases where alternative diagnoses cannot be fully excluded because of limited diagnostic capacity should be regarded as probable paradoxical TB–IRIS. In these probable cases, should resolution of clinical or radiological findings of the suspected IRIS episode occur without a change in TB treatment or ART having been made, they could then be reclassified as paradoxical TB–IRIS cases. Reproduced and modified from [13] with permission from the publisher.

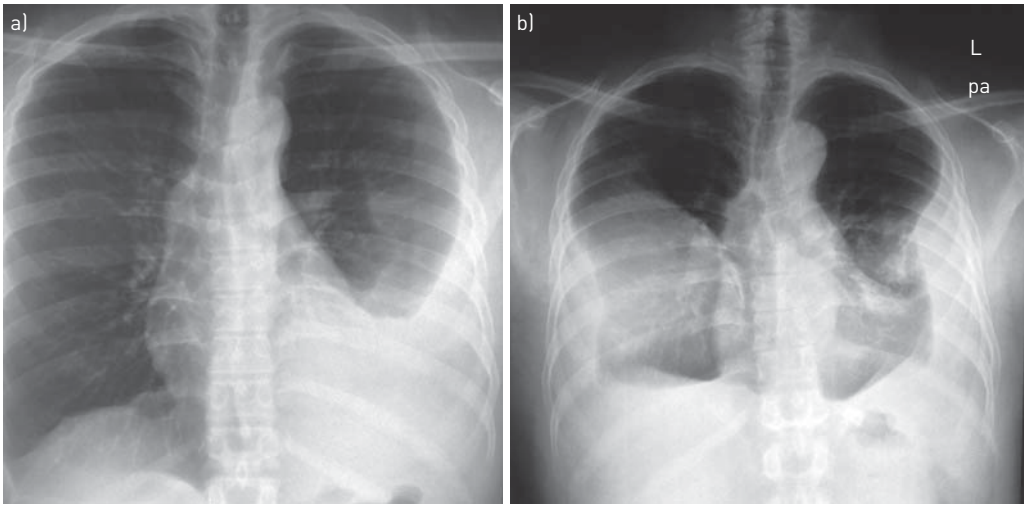


Figure 1. Paradoxical pulmonary TB-IRIS. a) Chest radiograph from a 32-year-old African male with loculated left pleural effusion and multiple paravertebral fluid collections extending into the right psoas muscle. Paravertebral fluid sampling revealed *Mycobacterium tuberculosis* sensitive to rifampin. He was initiated on TB therapy and ART (tenofovir/lamivudine/efavirenz) but presented 6 weeks later with acute kidney injury, dyspnoea, poor tolerance and fever. b) A further chest radiograph revealed worsening bilateral loculated effusions. Incision and drainage with biopsy revealed granulomas with culture-negative exudative fluid. ART and TB therapy were continued along with adjunctive corticosteroid therapy for 1 month. The patient tolerated therapy continuation and improved modestly, although the organised pleural effusions resulted in persistent restrictive pulmonary defects. Image courtesy of J. Venturas, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa.

morbidity contributed to the design of large clinical trials to examine the optimal timing of TB and ART initiation.

The SAPIt (Starting Antiretroviral Therapy at Three Points in Tuberculosis) trial randomised 642 HIV/TB co-infected South African patients with $CD4^+$ cell counts $<500 \text{ cells} \cdot \text{mm}^{-3}$ to three groups: 1) ART initiation within 4 weeks of TB treatment initiation (early integrated treatment group); 2) ART initiation within 4 weeks of completion of intensive phase of TB treatment (late integrated treatment group); and 3) ART initiation within 4 weeks after TB treatment completion (sequential treatment group) [45]. Consistent with prior observations and IRIS case definitions, patients in the early integrated HIV/TB treatment group experienced significantly higher incidence of TB-IRIS compared with the sequential and late treatment groups with overall incidence rates of 19.5, 7.5 and 8.1 per 100 person-years, respectively ($p < 0.001$). The incidence was even more notable in patients with $CD4^+$ cell counts $<50 \text{ cells} \cdot \text{mm}^{-3}$, with rates of 45.5, 9.7 and 19.7 per 100 person-years, respectively. The dedicated IRIS analysis documented 21.7% (43 out of 198), 11% (17 out of 164) and 13.7% (19 out of 139) of patients in the early, late and sequential treatment groups, respectively [46]. These data support prior conclusions that patients with lower $CD4^+$ counts (often $<100 \text{ cells} \cdot \text{mm}^{-3}$) are at increased risk for IRIS, including TB-IRIS [12, 41].

The CAMELIA (Cambodian Early *versus* Late Introduction of Antiretrovirals) trial was a second, large prospective, randomised controlled trial designed to determine the effect of earlier (2 weeks following TB treatment) *versus* later (8 weeks following TB treatment initiation) initiation of ART [47]. Important differences from the SAPIt trial included the enrolment of patients with $CD4^+$ cell counts $<200 \text{ cells} \cdot \text{mm}^{-3}$ and the lack of a sequential treatment group. The CAMELIA trial also demonstrated an increased incidence of TB-IRIS

with earlier ART treatment (HR 2.51, 95% CI 1.78–3.59; $p < 0.001$) with 36% and 16% of patients experiencing TB–IRIS in the early and late ART groups, respectively. Despite the increased risk of TB–IRIS, the early ART group demonstrated improved survival compared with later ART initiation. Further analysis revealed extrapulmonary or disseminated TB, a $CD4^+$ count $< 100 \text{ cells} \cdot \text{mm}^{-3}$, and an HIV RNA level $> 6 \log_{10} \text{ copies} \cdot \text{mL}^{-1}$ to be significantly associated with TB–IRIS risk [48].

A third study, the ACTG A5221 STRIDE study, examined the incidence of TB–IRIS in a similar way to the CAMELIA study, with the early (within 2 weeks of TB treatment) *versus* late (after 8–12 weeks of TB treatment) group but without a sequential treatment group [49]. This trial reiterated the higher occurrence of TB–IRIS in the early treatment group, albeit with lower estimates (10.4% early ART *versus* 4.7% late ART) [48]. This may be reflective of the fact that the CAMELIA and SAPIt trials had higher overall rates of smear-positive TB as a result of study eligibility, while the STRIDE study allowed the enrolment of “probable TB” patients. Within smear-positive TB patients with low ($< 50 \text{ cells} \cdot \text{mm}^{-3}$) $CD4^+$ counts, TB–IRIS rates were comparable. The STRIDE trial also recruited patients with $CD4^+$ cell counts $< 200 \text{ cells} \cdot \text{mm}^{-3}$, similar to the CAMELIA study rather than the $< 500 \text{ cells} \cdot \text{mm}^{-3}$ of the SAPIt trial.

In summary, these three recent large trials, designed to determine the optimal timing of ART initiation in patients co-infected with TB, have provided valuable insight into the true potential burden of IRIS in resource-limited settings. In HIV/TB co-infected patients who constitute the vast majority of co-infected patients initiating ART, the syndrome can be expected to occur in ~10–20% of patients. It should be noted that these TB–IRIS estimates are derived from carefully designed and highly resourced clinical trials. While they provide invaluable incidence estimates and identification of potential risk factors for the practicing clinician, the incidence of IRIS outside of these study settings is likely to vary considerably according to diagnostic capabilities and clinical practices. Paradoxical TB–IRIS can be expected to occur in such patients 17–29 days following ART initiation [46, 49], providing a relatively narrow window and an opportunity to increase clinical monitoring and clinical protocols. Finally, these estimates are restricted to patients with known or highly suspected HIV/TB co-infection at ART initiation and thus focus on paradoxical TB–IRIS and not the unmasking form, which suffers from the additional aforementioned diagnostic and definition difficulties.

Clinical presentation and management

In the SAPIt trial, new onset or worsening pulmonary infiltrates and/or respiratory symptoms dominated the clinical presentation of TB–IRIS with 59 (74%) out of 80 IRIS patients presenting with these complaints. Pleural effusions and thoracic lymphadenopathy also contributed to the respiratory presentation of the syndrome (8–12% of patients). Interestingly, although fever is classically described in IRIS and often included in IRIS definitions as a constitutional symptom, it was uncommon (two (2.5%) out of 80) and confined to those in the early integration treatment group [46]. This is in contrast to the CAMELIA trial, where fever was present in 68% of paradoxical TB–IRIS cases, but aligns with a reported high incidence of new or worsening chest radiography and lymphadenopathy (53% and 77%, respectively) as presenting respiratory symptoms [48]. Temporal and abrupt onset of extreme symptoms, such as acute respiratory failure, acute respiratory distress syndrome, tuberculous pleural effusions, ascites, and paratracheal lymphadenopathy and

compression [36, 37, 48, 50], are fortunately uncommon but highly support the diagnosis of unmasking or paradoxical pulmonary TB-IRIS.

Although some series report significant IRIS-associated mortality [51], the overwhelming majority of data from prospective trials documents a low mortality (<2–4%) [12, 46, 48, 49, 52]. However, IRIS significantly contributes to increased morbidity, including increased hospitalisation rates and resource utilisation [12, 46, 51]. In the STRIDE trial, 72% of patients were classified as having moderate-to-severe IRIS and 31% were hospitalised. Despite the potential morbidity, its occurrence should not preclude the initiation and widespread use of ART. This is supported by both retrospective and prospective studies, as well as decision-analyses [42, 44, 45, 47, 53, 54]. Finally, the diagnosis of IRIS often requires considerable diagnostic infrastructure, including chest radiographs, computed tomography and/or ultrasound, as well as procedurally adept clinicians and supporting pathology and microbiology personnel. These capabilities are often absent or restricted in resource-limited countries which complicates the diagnosis and estimates of TB-IRIS in clinical practice.

Although cessation of ART may be considered in severe, rare, life-threatening presentations (*i.e.* airway compromise due to extrinsic lymphadenopathy compression, severe expanding central nervous system (CNS) tuberculomas, *etc.*), ART can safely be continued in the majority of cases. Evidence for this arises from the aforementioned SAPiT trial [45]. Although paradoxical TB-IRIS incidence was higher in the integrated HIV/TB arms, a lower mortality was observed compared with the sequential treatment arm (integrated therapy group: HR 0.44, 95% CI 0.25–0.79; $p=0.003$). The CAMELIA trial also observed a low (3.8%) IRIS-attributable mortality, with the majority of symptoms (95.5%) resolving with little to no intervention. Fatal cases are usually limited to the aforementioned extreme presentations or to IRIS involving profound inflammation within a confined immunological compartment, as is seen with TB and cryptococcal meningitis [55, 56]. In these cases, cessation of ART and initiation of steroids is often necessary.

Nonsteroidal anti-inflammatory drug use is anecdotally reported in TB-IRIS. However, the use of corticosteroids has received the most attention, given their more potent and broad immunomodulatory effects. The strongest evidence for corticosteroid therapy arises from the first randomised controlled trial in TB-IRIS. In this South African study, 110 patients with mild-to-moderate TB-IRIS restricted to lymph node enlargement, cold abscesses, serous effusion or radiographic pulmonary infiltrate were randomised to either corticosteroids (prednisone $1.5 \text{ mg}\cdot\text{kg}^{-1}$ for 2 weeks followed by $0.75 \text{ mg}\cdot\text{kg}^{-1}$ for 2 weeks) or no-steroid therapy. Clinical end-points included cumulative hospitalisation days and outpatient therapeutic procedures. No difference in mortality between groups was observed. For the cumulative primary end-points, treatment with prednisone favoured a better response (median (interquartile range) hospitalisation: placebo 3 (0–9) days *versus* prednisone 1 (0–3) days; $p=0.046$). Symptom scores, pulmonary infiltrate improvement at weeks 2 and 4, and reduction in CRP levels all favoured prednisone therapy [57]. Given these results and the lack of any specific immunomodulatory therapy for IRIS, corticosteroids are used with or without nonsteroidal anti-inflammatory drugs in clinical practice. While 54.1% received corticosteroids in the STRIDE trial, use was more modest in the SAPiT (9.4%) and CAMELIA (14.8%) trials, though the latter used nonsteroidal anti-inflammatory drugs in over one-third of IRIS cases (35.5%). This usage range is probably reflective of the focus on smear-positive pulmonary TB in these trials and of the relatively uncommon severe pulmonary manifestations of IRIS warranting aggressive immunosuppressive therapy. In contrast, large case series examining neurological TB-IRIS report corticosteroid use in 91%

of patients experiencing CNS tuberculomas, meningitis and radiculopathies [56]. Thus, the decision to use corticosteroids is often subjectively based on the severity of the illness and the location of involvement.

Other pulmonary IRIS manifestations

Although far less common than either form of TB-IRIS, other pulmonary IRIS manifestations are important to consider in the HIV patient initiating ART (table 2). As with extrapulmonary IRIS manifestations, aetiologies can generally be infectious or noninfectious. Due to the lower frequency of occurrence, data and recommendations are considerably more limited and rely on case reports and individualisation of therapy.

MAC-associated IRIS

MAC-associated IRIS was one of the earliest reported manifestations of the syndrome due to its higher incidence and the earlier implementation of ART in developed countries [10]. In contrast to TB, which predominantly presents as a paradoxical form, MAC is often unsuspected in patients initiating ART and frequently presents as unmasking IRIS. When suspected, it is often difficult to diagnose, requiring long blood and sputum culture incubation times and more invasive procedures, such as bone marrow biopsies. Its true incidence is unknown due to differences in patient populations, geographic distribution and historical ART coverage.

In a similar way to TB, MAC-associated IRIS presents most commonly with lymphadenopathy, although abdominal and musculoskeletal abscesses are also possible. Pulmonary involvement occurs in ~20–25% of MAC-associated IRIS cases, with cavitation, infiltrates, mediastinal/hilar lymphadenopathy and endobronchial lesions all possible [38, 76]. MAC-associated IRIS also tends to present with suppuration of lymph nodes and intense localised inflammation [10]. Presentation also tends to be later after ART initiation, with a median of 4 weeks but with a wide range (interquartile range 2–8 weeks, range 1–52 weeks) [38].

Table 2. Summary of the pulmonary manifestations of IRIS

Infectious
Tuberculous pleural effusions [2, 6, 12, 50]
TB systemic inflammatory response and adult respiratory distress syndrome [36, 58]
TB cystic lung disease [59]
<i>Streptococcus pneumoniae</i> empyema [60]
<i>Mycobacterium celatum</i> disease [61]
<i>Cryptococcus neoformans</i> cavitory pneumonia and pneumonitis, and mediastinal lymphadenopathy [62–64]
<i>Histoplasma capsulatum</i> [65]
<i>Mycobacterium kansasii</i> pneumonitis and respiratory failure [37]
<i>Mycobacterium xenopi</i> pneumonia and pulmonary cavitation [66]
CMV pneumonitis [60]
Necrotising pulmonary aspergillosis [67, 68]
<i>Mycobacterium avium-intracellulare</i> pleural effusion [69]
Noninfectious
Pulmonary sarcoidosis [70, 71]
Interstitial lymphoid pneumonitis [72]
Kaposi's sarcoma [73–75]

Thus, the timing of an unmasking clinical event can further direct suspicion towards MAC-associated IRIS. Although not definitive, localised extrapulmonary suppurative lymphadenopathy in a patient with smear-negative disease can clinically suggest a non-tuberculous aetiology. In all cases of suspected TB–IRIS, MAC should be considered, particularly in more developed countries where its frequency is considerably higher than in resource-limited settings. Implications for its presence include prolonged treatment with treatment regimens that include the use of macrolide antibiotics. Due to intense, localised disease MAC-associated IRIS is often treated with and responds to corticosteroids and initiation or continuation of ART [10, 76]. As with other IRIS aetiologies, presentations may be severe and require discontinuation of ART [77].

Other infectious manifestations

Of the infectious aetiologies, pulmonary *Pneumocystis jirovecii* and *Cryptococcus neoformans* are the two most common aetiologies of pulmonary IRIS [78–81]. Both aetiologies may present early and abruptly with a range of respiratory symptoms and findings, such as pulmonary nodules and infiltrates. These nonspecific symptoms present a diagnostic challenge to the practicing clinician, particularly those with limited resources and in areas with endemic opportunistic infections such as TB. In these settings, the co-existence of multiple opportunistic infections, particularly in severely immunosuppressed patients ($CD4^+$ cell counts $<50 \text{ cells}\cdot\text{mm}^{-3}$), should be considered and adds complexity to IRIS diagnosis and management. Other uncommon pulmonary infectious complications are largely confined to case reports and case series (table 2).

Noninfectious pulmonary IRIS manifestations

While more systemic autoimmune cases of IRIS have been described, noninfectious pulmonary IRIS manifestations are restricted to sarcoidosis and Kaposi's sarcoma [73–75, 70, 71]. While uncommon, both of these pulmonary complications can be severe, particularly if extrapulmonary systemic complications occur. Systemic sarcoidosis can be exacerbated and include granulomatous inflammation, hepatitis, nephritis and alveolitis as extreme manifestations [70]. Pulmonary Kaposi's sarcoma commonly and somewhat characteristically presents with ill-defined pulmonary nodules and interlobular septal thickening, as well as pulmonary consolidation, ground-glass opacities, lymphadenopathy and pleural effusions [75]. In a prospective trial in Mozambique, Africa, 69 HIV-infected patients with Kaposi's sarcoma were observed following ART initiation. Of these, eight (11.6%) out of 69 patients developed IRIS–Kaposi's sarcoma at a notable 13.8 weeks following ART initiation. Risk factors included pre-treatment of Kaposi's sarcoma, detectable plasma Kaposi's sarcoma DNA, anaemia and increased HIV RNA viral load. Consistent with the management of other IRIS aetiologies, ART was continued in the majority and when combined with systemic chemotherapy, a partial or complete clinical response was documented in five out of eight cases.

Conclusion

In summary, increasing recognition, diagnosis and management of HIV-associated IRIS has had a significant impact on the practicing respiratory clinician. IRIS has not only changed the clinical landscape for how one approaches the patient with respiratory symptoms and chest findings, but also the management of such patients. Driven by public health and clinical concerns regarding TB–IRIS in the HIV/TB co-infected patient, the field of HIV and TB have

learned a great deal on optimising the timing of ART therapy in this population. Fortunately, IRIS-attributable mortality is low and concerns for the syndrome should not delay ART initiation in this severely immunosuppressed population. However, pulmonary and nonpulmonary morbidities remain significant and should be an area of future research in order to optimise the impact of IRIS on existing limited health systems. Until more definitive immunological mechanisms are identified, specific interventions for disease management will remain limited and individualised at the single patient level. Finally, IRIS has contributed to and should draw from the science of the broader field of immune reconstitution to further our understanding of the disease in order to prevent its occurrence and minimise its impact on HIV-infected patients.

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